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PRACTICAL GUIDES AND CLINICAL RECOMMENDATIONS – WHY ARE THEY IMPORTANT?

Helena Canhão*

This issue of Acta Reumatologica Portuguesa presents two articles with orientations and guidance devoted to clinical practice: «Prophylaxis of hepatitis B reactivation with immunosuppressive therapy in rheumatic diseases. Orientations for clinical practice»[1] from J Nunes et al and «Physiotherapy in rheumatoid arthritis: development of a practice guideline»[2] by EJ Hurkmans et al.

The first one is a joined publication from Gastroenterology/Hepatology and Rheumatology and discusses a very hot and challenging subject, hepatitis B virus (HBV) infection reactivation in patients undergoing immunosuppressant therapy. Authors begin by saying that the reactivation of infection with hepatitis B virus is a potentially serious complication of immunosuppression, but can be identified and efficiently prevented. They also give a well documented background, tables and figures describing the natural stages of chronic hepatitis B virus infection, the diagnostic markers in hepatitis B virus infection, the definitions and diagnostic criteria used in HBV infection and the mechanism of HBV reactivation in patients under immunosuppressant therapies. The paper was then structured based on practical questions and answers: Who should be screened for HBV infection? How to screen? The differences between HBV therapy, prophylaxis and monitoring. Which rheumatic patients should start therapy and/or prophylaxis of HBV reactivation? When to start and to stop prophylaxis? Which drugs should be used? The answers to these questions established the rationale for the recommendations and practical guide issued. The summary at the end is simple and clear, what makes this article very useful for clinical practice.

The second article constitutes a practice guideline developed in Netherlands also with collaborations from different fields (Rehabilitation, Ortopedics and Rheumatology), and it was presented with the aim of improving the quality of the physiotherapy management in patients with rheumatoid arthritis (RA). The recommendations were developed based on current scientific evidence and best practice using the International Classification of Functioning, Disability and Health (ICF) and the ICF core sets for RA. At the end this physiotherapy practice guideline includes seven recommendations on the initial assessment, treatment and evaluation for patients with RA.

These articles represent two examples of how useful and practical recommendations can be. Ideally, guidelines should be supported by a thorough systematic literature review, should include, in its discussion and elaboration, experts from the different areas that are relevant for the debated issue, should be relevant for clinical practice, should previously identify the groups of physicians to be targeted, should be simple, practical and easily understandable, should have an implementation plan and a plan for the future evaluation of their impact in clinical practice and should be reviewed whenever new knowledge and evidence imply changes on the previous standard of care.

It is not an easy task to put together all these conditions but when it succeeds the output can constitute a major help to daily practice.

Sometimes legal issues related with guidelines are raised. Are guidelines a rule? Should they be mandatory? If physicians choose not to follow the guidelines could they be accused of malpractice?

Can recommendations be more harmful than useful?

In my personnel point of view, recommendations and practical guides are unique in the sense that they potentially gather the most relevant published body of information, assign the level of evidence, process and summarize it, and translate the output into simple and useful practical sentences and guidance. However, they should also be looked as general guides; in fact, the individual patient can show specific features for which general guidelines do not always apply. But in the end recommenda-

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tions and guiding documents can be an outstanding support for physicians in their daily practice. Enjoy these 2 articles!

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VASCULITIC NEUROPATHY

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Eva Mariz*, Francisco Ventura*

Abstract

Vasculitic neuropathy corresponds to the occurrence of vasculitis at the level of *vasa nervorum*, resulting in ischemic damage of the peripheral nerve and axonal degeneration.

Vasculitic neuropathy commonly occurs in association with systemic diseases and may be the initial manifestation or arise in the course of established disease. Although rare, vasculitis can be confined to the peripheral nervous system – non--systemic vasculitic neuropathy.

This paper aims to review the classification, diagnosis and treatment of vasculitic neuropathy.

Keywords: Vasculitic Neuropathy; Vasculitis; Peripheral Nervous System.

Introduction

Vasculitis is defined as vascular wall inflammation and may occur as a primary phenomenon or secondary to an established disease. It can involve vessels of different diameters and different organs, affecting the peripheral nervous system in 60-70% of patients with some systemic vasculitic syndromes[1]. Systemic vasculitides are divided into two categories: primary systemic vasculitis, where there is no identified etiology, and secondary systemic vasculitis, which occurs in the context of other pathologies such as connective tissue diseases, infectious diseases, neoplastic or induced by drugs.

Primary systemic vasculitides are classified based on the diameter of the vessels involved. Vasculitis most associated with vasculitic neuropathy are those involving the pre capillary arteries in the nerves, ie, Polyarteritis *Nodosa*, Wegener's Granulomatosis, Microscopic Polyangiitis and Churg--Strauss syndrome[2,3].

Secondary systemic vasculitides associated with neuropathy can occur in the context of:

a) Connective tissue disorders as Rheumatoid Arthritis, Systemic Lupus Erythematosus (SLE) or Sjögren Syndrome,
b) Infections such as Hepatitis C, Human immunodeficiency virus (HIV), Cytomegalovirus (CMV) and Parvovirus B19,
c) Neoplasms as non-Hodgkin lymphoma, small cell carcinoma and gastrointestinal tumors,
d) Drugs[3].

In a minority of cases the vasculitis is confined to the nerve, denominated non-systemic vasculitic neuropathy[4,5] (Figure 1 and Table I).

Physiopathology

Vasculitis is defined as inflammation of a blood vessel, with consequent destruction of the vascular wall and tissue ischemia. Histologically, it is characterized by fibrinoid necrosis of the vascular wall.

In vasculitic neuropathy, there are two mechanisms of induction of vasculitis in the *vasa nervorum*: 1) deposition of immune complexes and 2)

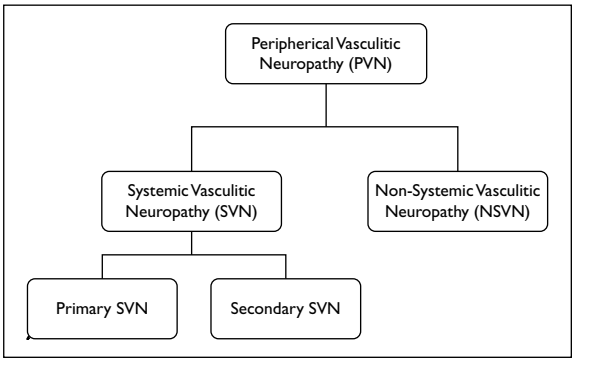

Figure 1. Classification of peripheral vasculitic neuropathy

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Table I. Classification of Systemic Vasculitic Neuropathy

Primary Systemic Vasculitis (60%):
- Churg-Strauss syndrome (20%)
- Polyarteritis Nodosa (18%)
- Wegener's granulomatosis (12%)
- Microscopic polyangiitis (7%)
- Cryoglobulinaemia (2%)
- Henoch-Schönlein purpura (1%)

Secondary Systemic Vasculitis (25%):
- Connective tissue disease (17%):
  Rheumatoid arthritis, Systemic Lupus Erythematosus, Sjögren syndrome
- Infection (4%):
  Hepatitis C and B, HIV, CMV, Parvovirus B19
- Malignancy (3%):
  Non-Hodgkin lymphoma, small cell carcinoma of the lung and digestive cancers.
  Others (1%):
  Sarcoidosis, drugs, Diabetes Mellitus

cell-mediated immunity[6].

1) Deposition of immune complexes (IC): circulating antibodies bind to endogenous or exogenous antigens forming IC, these will be deposited in the vascular wall and activate the complement, forming factors C3a and C5a, which are chemotactic for neutrophils.

Neutrophils infiltrate the vascular wall, phagocyte the IC and release proteolytic enzymes and oxygen free radicals that will destroy the vascular wall.

This mechanism is associated with vasculitis secondary to infection, connective tissue diseases, cancer, drugs and cryoglobulinemia[3,6].

2) Cell-mediated immunity: T cells in circulation recognize antigens associated with endothelial cells that act as antigen presenting cells. This interaction leads to increased expression of cell adhesion molecules and release of chemotactic cytokines [eg. Tumor Necrosis Factor (TNF) alpha], which in turn recruit and activate neutrophils and lymphocytes with subsequent inflammation and destruction of the vascular wall[6,7]. This mechanism occurs in vasculitis associated with anti-neutrophilic cytoplasmatic antibodies (ANCAs).

The end result of both processes is the induction of immunological inflammation and necrosis of vessel wall, compromise of the lumen and peripheral nerve ischemia. Ischemia will cause focal and asymmetric axonal degeneration, and this process is more frequent in myelinated fibers than in non-myelinated fibers.

Clinical Manifestations

Clinical manifestations of vasculitic neuropathy can be divided into neurologic and systemic manifestations.

Neurological manifestations include pain, dysesthesia, paresthesia and decreased muscle strength in the territory of a nerve, usually of acute or subacute onset. The first nerves to be affected are the longest and with progression from distal to proximal. The nerves most commonly involved are the peroneal, tibial, ulnar, median and radial[8]. It is a sensory or sensory-motor neuropathy, with pure motor neuropathy being extremely rare. In vasculitic neuropathy, there are three patterns of peripheral nerve injury: mononeuritis multiplex, asymmetric polyneuropathy and distal symmetric polyneuropathy.

Mononeuritis multiplex is characterized by injury of two or more nerves in separate areas. A common clinical presentation is the foot drop by infarction of peroneal nerve, or the hand drop by damage of radial nerve. This is the most specific form of presentation of vasculitis, occurring in approximately 10-15% of vasculitic neuropathies, however it is important the differential diagnosis with other pathologies such as leprosy, Lyme disease or diabetes[8] (Table II).

With progressive involvement of various nerves we have overlapping mononeuropathies, resulting in a pattern of asymmetric polyneuropathy. This form of presentation is more frequent in vasculitic neuropathy, accounting for three quarters of patients.

Distal symmetric polyneuropathy is the less frequent form of presentation of vasculitic neuropathy. It usually presents with sensorimotor disturbances that have a symmetrical «stocking and glove» distribution[8].

Systemic manifestations include constitutional symptoms and specific organ symptoms. Constitutional symptoms such as weight loss, fever and malaise, are more common in systemic vasculitic neuropathies, but may also be present in 15-40% of non-systemic vasculitic neuropathy[9].

Specific organ symptoms occur only in systemic vasculitic neuropathies. The most characteristic skin manifestations are purpura, ulcers or nodules. Respiratory system involvement can be translated

Table II. Differential Diagnosis of Mononeuritis Multiplex

- Acute or chronic inflammatory demyelinating polyneuropathy
- Lyme disease
- Leprosy
- Diabetes mellitus
- Neurofibromatosis
- Neoplasia with nerve invasion
- Multiple cholesterol embolism
- Vasculitic neuropathy

as rhinitis, purulent rhinorrhea, asthma and hemoptysis. Gastrointestinal involvement can present as abdominal pain and gastrointestinal bleeding, musculoskeletal involvement as arthralgia, myalgia and arthritis, and renal involvement as hematuria, proteinuria, or hypertension[2,3].

Primary Systemic Vasculitic Neuropathy

Neuropathy occurs mainly in vasculitis with involvement of arteries of medium and small size, being very rare in vasculitis with involvement of large vessels only (eg, Takayasu arteritis). Polyarteritis *nodosa* is a vasculitis of medium and small arteries. Vasculitic neuropathy is one of its classification criteria of ACR 1990 and it is present in 50-75% of patients[3,10]. Clinical features associated with this systemic vasculitis are: livedo reticularis, palpable purpura, digital ischemia, arthralgia and nephropathy. The presence of microaneurysms and occlusion of small and medium arteries are angiographic characteristics of this vasculitis.

Churg-Strauss syndrome is a primary vasculitis of small and medium sized vessels, associated with peripheral eosinophilia and ANCA with anti--mieloperoxidase (MPO) specificity. Clinical characteristics often associated are: palpable purpura, rhinitis, asthma, and arthralgia. Neuropathy appears in about 80% of patients, and is also one of the ACR 1990 classification criteria[8,10].

Microscopic polyangiitis is a necrotizing vasculitis involving small vessels, associated with perinuclear pattern ANCA (p-ANCA) in approximately 60-80% of cases. The main clinical features are arthralgia, alveolar hemorrhage, and rapidly progressive glomerulonephritis[1,10]. Vasculitic neuropathy is present in 70% of patients[10].

Wegener's granulomatosis (WG) is a vasculitis of small vessels, associated with ANCA with anti-proteinase 3 specifity (PR3) in approximately 90% of cases. Neuropathy is present in 15-40% of patients and the typical clinical characteristics include destruction of the nasal sinuses, oral ulcers, arthralgias, pulmonary infiltrates and glomerulonephritis[3,11].

Cryoglobulinemia is a small vessel vasculitis associated with cryoglobulins and it presents commonly with palpable purpura, skin ulcers and arthralgia[12]. Neuropathy occurs in about two thirds of patients[12].

Henoch-Schönlein purpura is a vasculitis of small vessels which may also involve the *vasa nervorum* causing neuropathy. Clinical features associated with this vasculitis are: palpable purpura, arthritis, abdominal pain and nephropathy[1,3].

Systemic Vasculitic Neuropathy Secondary to Connective Tissue Diseases

In Rheumatoid Arthritis (RA), vasculitis involves mainly medium and small arteries. Vasculitic neuropathy occurs in about 10% of patients, presenting as mononeuritis multiplex or symmetric sensory-motor polyneuropathy[13]. It is more common in patients with severe RA (nodules, joint erosions and deformities), with long standing disease and with high rheumatoid factor (RF) titers[13]. Clinical features associated with rheumatoid vasculitis are skin ulcers, digital ischemia, pericarditis and mesenteric vasculitis[13].

In systemic lupus erythematosus (SLE), neuropathy appears in approximately 5% of patients[14]. The most common presentations are mononeuritis multiplex or symmetric sensory-motor polyneuropathy[14,15]. One large study of patients with SLE showed an association between vasculitis and Raynaud's phenomenon, serositis, myocarditis, leukopenia and antiphospholipid antibody syndrome[15]. In this study peripheral neuropathy was the most common initial presentation of vasculitis, aside from cutaneous lesions. Patients with vasculitis had longer disease duration and younger age of SLE onset[15].

Vasculitic neuropathy is reported in 10% of patients with Primary Sjögren Syndrome[16]. It commonly presents as a distal symmetric sensorimotor polyneuropathy, with predominant sensory characteristics[16].

Vasculitic neuropathy secondary to infection

Infections most often associated with vasculitic neuropathy include: Hepatitis B and C, HIV, CMV,

and parvovirus B19[17].

Hepatitis B (HBV) can be associated with Polyarteritis *Nodosa* (PAN), with the clinical picture similar to idiopathic PAN. The prevalence of HBV-related PAN has declined over the past few years to 20%[10]. Vasculitis usually appears within the first 12 months of infection. Neuropathy appears in about 83% of patients[10,17].

Hepatitis C has a strong association with Mixed Cryoglobulinemia, with 80 -90% of such patients being positive for anti-HCV antibodies. The most frequent clinical features are purpura, arthralgias, neuropathy and glomerulonephritis[17].

Vasculitis in HIV infection can be directly related to HIV or secondary to an opportunistic infection, particularly to CMV. Neuropathy occurs in less than 1% of patients, presenting mainly as a distal symmetric sensory polyneuropathy[18]. It may arise at any stage of the disease[18].

Parvovirus B19 infection can induce a vasculitis of small vessels, mimicking Henoch-Schönlein purpura, in about 1% of patients[17].

Vasculitic neuropathy secondary to malignancy

Cancers most often associated with vasculitic neuropathy are: non-Hodgkin lymphoma, small cell carcinoma of the lung and digestive cancers. The clinical picture of the neuropathy is similar to that of primary vasculitis, with the exception of neuropathy secondary to lymphoma, which commonly involves the central nervous system (CNS). Other manifestations of these neuropathies are weight loss, asthenia and anorexia[3,8].

Vasculitic neuropathy secondary to sarcoidosis

Sarcoidosis can cause granulomatous vasculitis at the level of *vasa nervorum* resulting in vasculitic neuropathy. The usual form of presentation is an acute or subacute mononeuritis multiplex, but a sensorimotor polyneuropathy can also be present[19]. The main clinical characteristics associated with this disorder are erythema nodosum, arthralgias, hilar adenopathy and CNS involvement[19].

Vasculitic neuropathy secondary to diabetes *mellitus*

Vasculitic neuropathy secondary to diabetes *mellitus*, also known as lumbosacral radiculo plexopathy, occurs in a small percentage of patients, especially in those over 50 years old [20]. It is characterized by acute or subacute pain and muscle weakness at lower limb, proximal and unilateral, progressing to bilateral[20].

Vasculitis neuropathy secondary to drugs

Several drugs can induce vasculitis, involving more commonly the small vessels of the skin, and less frequently the peripheral nerves. The drugs most commonly associated with the induction of vasculitis are hydralazine, propylthiouracil and leucotriene antagonists[21].

Non-systemic vasculitic neuropathy

Non-systemic vasculitic neuropathy comprises approximately 15% of the cases of vasculitic neuropathies[7]. It was first described in 1938 by Kernohan and Woltman, but only in 1987 was introduced the term of non-systemic vasculitic neuropathy by Dyck and colleagues[4].

In 2004 Collins proposed the following diagnostic criteria: (1) clinical evidence of neuropathy, (2) electrodiagnostic changes consistent with axonal neuropathy, (3) nerve or nerve/muscle biopsy diagnostic of vasculitis, (4) without clinical, laboratory or radiological evidence of non-neuromuscular involvement, (5) non-identified etiology, and (6) no systemic disease predisposing to vasculitis (e.g, connective tissue disease, malignancy, cryoglobulinemia)[7].

As with systemic vasculitic neuropathy, non-systemic vasculitic neuropathy most commonly presents as mononeuropathy multiplex. The evolution is slower than in systemic vasculitic neuropathy, with better prognosis[7].

General symptoms, such as weight loss and fever, can be present in approximately 15-40% of patients. Sixty percent have mild to moderate increase in sedimentation rate. Thirty percent have anemia and 15% leukocytosis. Approximately 30% have positive ANA, 13% are RF positive and 11% have positive ANCA[22,23].

Several studies have shown that 6-37% of patients develop systemic vasculitis[22,24].

Diagnosis

The diagnosis must be based on clinical history and physical examination, including neurological examination, laboratory studies, nerve conduction and electromyography studies, and nerve biopsy[2,7]. In the clinical history it is important to search for peripheral neurologic symptoms, such as dysesthesia, paresthesia and muscle weakness. A careful history of organ/system symptoms should be taken, in order to rule out respiratory, cardiovascular,

musculoskeletal, genitourinary, gastrointestinal or cutaneous involvement.

On physical examination is important to perform general and neurological examination with identification of territories involved, evaluating sensitivity, muscle strength and tendon reflexes. Laboratory tests can exclude or confirm the presence of systemic disease and should always be guided by clinical history and physical examination. The initial analytical study should include complete blood count, erythrocyte sedimentation rate, C-reactive protein, serum creatinine, transaminases, urinary sediment study, and in selected cases, antibodies to hepatitis B, C and HIV, CMV and Parvovirus B19 serology, angiotensin converting enzyme, antinuclear antibodies, anti-ds DNA, ANCA, RF, anticyclic citrullinated protein antibodies (anti-CCP), anti SSa and SSb, cryoglobulins and complement.

Electrophysiological studies reveal axonal injury involving multiple individual nerves. Nerve conduction studies show low amplitude muscle action potentials, with normal or slightly decreased conduction velocity. Electromyographic evaluation of the affected muscles reveals fibrillation potencials and decreased recruitment of motor unit potencials[8].

Nerve biopsy can provide a definitive diagnosis when it shows infiltration of inflammatory cells in the vascular wall associated with necrosis of the wall of *vasa nervorum*. However, this technique has a sensitivity of only 60% because the vasculitis lesions are focal. The combination of nerve and muscle biopsy increases the sensitivity of the nerve biopsy alone, being the most frequent combinations the sural nerve and gastrocnemius muscle, or peroneal nerve and peroneal muscle[4,6].

However, nerve biopsy is not always necessary for the diagnosis of vasculitic neuropathy, ie. in cases where the clinical presentation is compatible with vasculitic neuropathy and there is histological or angiographic evidence of vasculitis in another organ[2].

Treatment

Treatment of vasculitic neuropathy is initiated by the removal of precipitating factors in cases related to drugs, infection or malignancy, followed by immunosuppressive therapy, analgesics and physical rehabilitation.

Immunosuppressive treatment

NON-SYSTEMIC VASCULITIC NEUROPATHY

Given the paucity of randomized controlled trials for the treatment of non-systemic vasculitic neuropathies, the therapeutic decision is based upon the physician's clinical experience, on data from observational studies and extrapolation of results obtained in the treatment of systemic vasculitides.

REMISSION INDUCTION TREATMENT

Steroids are the first line treatment in non-systemic vasculitic neuropathy. It is recommended to start with prednisolone at a dose of 1 to 1.5 mg/kg/d for two months, or in severe cases, start with pulses of methylprednisolone 1g/d for 3-5 days[25]. Subsequently, prednisolone should be gradually tapered (10mg/week) up to 40mg/d, followed by 5mg/week up to 20mg/d, and by 1mg every two weeks up to 5mg/d. It is important to carefully monitor the patient, concerning an eventual worsening of the neuropathy itself or occurrence of early systemic symptoms[5,25].

Most authors recommend the combination of cyclophosphamide in the induction treatment of non-systemic vasculitic neuropathy. It can be used the oral (2mg/kg/d) or intravenous (750mg/m^2) route. Cyclophosphamide should be continued for 3-6 months, and later replaced by a less toxic drug[5,7]. Current available data suggest that pulse-dosing cyclophosphamide results in fewer adverse effects, like haemorrhagic cystitis and transitional cell carcinoma of the bladder, but carries an increased risk for relapses compared with oral cyclophosphamide[26].

MAINTENANCE TREATMENT

After induction treatment it is recommended to replace cyclophosphamide by azathioprine or methotrexate. Azathioprine should be started at a dose of 50mg/d increased gradually to 2-3 mg/kg/d. Methotrexate should be started with 15mg/week and gradually increased up to 25mg/week[5].

The maintenance treatment should be continued for one year after remission.

PRIMARY SYSTEMIC VASCULITIC NEUROPATHY/ /SECONDARY TO CONNECTIVE TISSUE DISEASES

In systemic vasculitic neuropathy the aggressiveness of therapy will depend largely on the involvement of major organs such as kidney and/or lung, not only on the peripheral nervous system involvement.

The first line treatment recommended is the combination of cyclophosphamide with corticos-

teroids. In the remission induction phase, three pulses of 1 g/d of methylprednisolone followed by prednisolone 1mg/kg/d associated with monthly intravenous cyclophosphamide (15mg/kg, max.1g). Maintenance treatment: cyclophosphamide pulses quarterly, or azathioprine (2-3mg/kg/d)[27,28].

VASCULITIC NEUROPATHY SECONDARY TO INFECTION

Chronic immunosuppressive treatment is contraindicated in vasculitic neuropathy secondary to viral infections. Corticosteroids may be used for short periods, 1mg/kg/d in the first week with a rapid tapering and suspension after two weeks.

The anti-viral treatment should be continued for at least 6 months, in case of hepatitis C with ribavirin and interferon alpha, and in hepatitis B with lamivudine.

In resistant cases, plasmapheresis is indicated for the removal of immune complexes[17].

NEW TREATMENTS

For patients with progressive disease in spite of optimal therapy, alternative options include anti-TNF alpha agents and rituximab[29].

Aggressive forms of vasculitis have been postulated to be the result of in appropriately increased production of TNF[29]. Inhibition of TNF seems to reduce inflammation and improve endothelial dysfunction in systemic vasculitis[30]. Reports of uncontrolled trials have suggested the efficacy of TNF inhibition in patients with Wegener's granulomatosis, rheumatoid arthritis or crioglobulin associated vasculitides, refractory to standard treatment[31-33].

Rituximab, a chimeric anti-CD20 antibody, induces the death of B cells. Rituximab has shown promising results in the treatment of cryoglobulinaemic vasculitis and rheumatoid arthritis[34]. Two small studies suggest improvement in neuropathic symptoms in patients with hepatitis C associated cryoglobulinaemic vasculitis[35].

A multicenter retrospective study with 65 patients showed that rituximab was effective as a remission induction therapy for refractory ANCA-associated vasculitis. This study also found that continuing immunosuppression did not reduce relapses, but re-treatment was effective and safe[36].

However, randomized controlled trials of rituximab for vasculitis have not been done.

ANALGESIC TREATMENT

Pain is present in almost all patients with vasculitic neuropathy and can be severe. Even after appropriate immunosuppressive treatment about 44-71% of patients have chronic pain[25]. The drugs recommended for treatment of pain in vasculitic neuropathy are: amitriptyline, carbamazepine, gabapentin, pregabalin and duloxetine[25,27].

PHYSICAL REHABILITATION

Physical rehabilitation should begin as early as possible.

In the initial stage, pending the axonal regeneration, rehabilitation is especially important to maintain joint range of motion and prevent muscle atrophy, with passive range of motion exercises consisting in progressive stretching. The use of braces or splints can also be recommended to enhance balance and posture[25].

Prognosis

The prognosis correlates directly with early diagnosis and treatment.

Several studies also showed better prognosis in combination treatment (cyclophosphamide and prednisolone) versus monotherapy with prednisolone[5,25,28].

Although there is no comparative study, the systemic vasculitic neuropathies have a worse prognosis than non-systemic vasculitic neuropathy, both in terms of survival, and of neurologic deficit[25].

Conclusion

Vasculitic neuropathy most often occurs in the context of a systemic disease, usually a primary systemic vasculitis or a connective tissue disease. Less often, vasculitic neuropathy presents in an isolated fashion, called non-systemic vasculitic neuropathy. The diagnosis is based on a careful history, complete physical examination and selected laboratory assays designed to diagnose or exclude a systemic disease.

Electromyography and nerve conduction studies are useful to distinguish nerve dysfunction from muscular disease and in identifying characteristic patterns of peripheral nerve disease.

The gold standard for the diagnosis of vasculitic neuropathy is a nerve biopsy, usually performed in conjunction with a muscle biopsy. Patients with biopsy proven vasculitis in other organ and pre-

sentation of nerve dysfunction typical of vasculitis do not require nerve biopsy.

Although corticosteroids remain the mainstay of treatment for vasculitic neuropathy, current treatments are becoming more disease specific. Prospective clinical trials of traditional and novel treatments are needed to identify indications and establish efficacy for immunosuppressant agents, intravenous immunoglobulin, and plasma exchange.

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PROPHYLAXIS OF HEPATITIS B REACTIVATION WITH IMMUNOSUPPRESSIVE THERAPY IN RHEUMATIC DISEASES. ORIENTATIONS FOR CLINICAL PRACTICE

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Abstract

Reactivation of infection with hepatitis B virus (HBV) is a potentially serious complication of immunosuppression, which can be identified and efficiently prevented. There have been an increasing number of cases of HBV reactivation in patients receiving immunosuppression in the context of rheumatic diseases such as rheumatoid arthritis or systemic lupus erythematosus. The recommendations in this area should be individualized taking into account two aspects: immunosuppressive regimens used (high or low risk of reactivation) and the different stages of HBV infection: chronic hepatitis B, inactive HBV carrier, occult hepatitis B infection defined by HB surface antigen (HBsAg) negative and antibody anti-HB core (anti-HBc) positive. In patients with rheumatic diseases that will start high risk immunosuppressive drugs, we propose a universal screening with serological tests for hepatitis B (HBsAg, anti-HBs and anti-HBc). Patients with chronic hepatitis B (HBsAg positive, HBV DNA ≥ 2000 IU/ml, elevated ALT) should initiate antiviral therapy. Inactive HBV carriers (HBsAg positive, HBV DNA <2000 IU / ml, normal aminotransferases) exposed to high risk immunosuppressive therapy should undergo prophylaxis of HBV reactivation. Prophylaxis should be started 2 to 4 weeks before the beginning of immunosuppressive therapy and maintained for at least 6 to 12 months after its suspension. It is recommended to use entecavir or tenofovir as first line antiviral agents. In inactive HBsAg carriers under low-risk immunosuppressive therapy and patients with HBsAg negative/anti-HBc positive (HBV infection in the past), the strategy should be monitoring of viral reactivation with aminotransferases and HBV DNA determination in every 6 months.

Keywords: Rheumatic Diseases; Hepatitis B Reactivation; Immunosuppression; Entecavir; Tenofovir.

Introduction

Hepatitis B virus (HBV) chronic infection is the leading cause of liver cirrhosis and hepatocellular carcinoma (HCC) in the world[1]. It is estimated that almost one third of the world population has been infected with the virus and about 350 million people are chronically infected[2]. In Portugal, about 1% of the population is a chronic carrier of HBsAg[3]. Hepatitis B infection is easily prevented by vaccination[4].

HBV infection is a heterogeneous disease with distinct phases, depending on age of infection, viral replication, immune response against the virus and liver damage. The evolution for chronicity is unusual in adults, with more than 99% clearing effectively the virus[5]. However, in most of these patients viral particles remain in the nucleus of the hepatocytes, and may be used as copies for viral replication under some circumstances, like immunosuppression[6]. If not detected and treated, viral reactivation can be severe and sometimes fatal.

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Given the increasing use of immunosuppressant, the potential serious effects of HBV reactivation and efficacy of prophylaxis, it is important to identify patients at risk and implement appropriate measures.

The aim of this paper is to review hepatitis B virus reactivation in patients under immunosuppression therapy for rheumatic diseases and to porpose prophylactic measures. This was made considering recent data available in the literature of rheumatic diseases and taking into account the experience obtained in other areas where there is more extensive knowledge on this subject, like hematology and oncology[7,8].

Hepatitis B virus infection

The natural stages of chronic hepatitis B virus infection

The natural history of chronic hepatitis B (CHB) infection is determined by the interplay between the virus and the host immune response[9,10]. According to this, it is possible to distinguish five phases:

- ***immune tolerant phase***. The immune system is not reacting against the virus. The virus replicates freely, hepatitis B e antigen (HBeAg) is positive, with very high levels of HBV DNA, (more than 10^8 IU/ml) but there is no liver damage and aminotransferases are normal.
- ***immune reactive phase***. The immune system controls the virus. Low serum HBV DNA levels are present, with increased or fluctuating levels of aminotransferases and moderate to severe liver necroinflammation.
- ***inactive HBV carrier phase***. Represents immunological control of the infection and is characterized by very low or undetectable serum HBV DNA levels, antibody against HBeAg (anti-HBe) positivity and normal aminotransferases. These patients have a very low risk of cirrhosis or HCC. HBV DNA is less than 2.000 IU/ml.
- ***HBeAg negative CHB phase***. This represents a later phase in the natural history of CHB infection, with the development of HBeAg negative variants. It is characterized by active hepatitis, with fluctuating levels of HBV DNA and aminotransferases.
- ***HBsAg negative phase***. This is the closest to cure of CHB infection and it is characterized by the presence of antibody against HBcAg (anti-HBc) with or without antibody against HBsAg (anti-HBs). In these patients, low-level of HBV replication occurs in the liver, but HBV DNA is generally not detectable in the serum (termed occult HBV infection)[11]. This occurs because during viral replication copies of covalently closed and circular DNA (cccDNA) are produced, and these remain in the nucleus of the hepatocytes, integrated in host DNA. It is considered that all HBsAg negative/anti-HBc positive individuals are potential HBV occult carriers. Although they have generally an excellent prognosis, an increasing number of viral reactivation cases have been reported in concomitantly immunossuppressed patients[12] or in the setting of organ transplants[13].

This late phase is indistinguishable from the recovery of an acute hepatitis B.

Diagnostic markers in hepatitis B virus infection

The diagnosis of HBV infection typically is based on the evaluation of serologic markers of HBV infection. The serologic markers allow the distinction between active (including acute or chronic hepatitis B) and past infection. It also identifies vaccinated and susceptible persons for acquiring HBV infection (Table I).

Definitions and diagnostic criteria used in HBV infection

In clinical practice, it is useful to classify patients with the following definitions: chronic hepatitis B, inactive HBsAg carrier and "resolved" hepatitis B[14,15] .

- *chronic hepatitis B* (active carrier of HBV) is defined as the presence of HBsAg (two determinations, 6 months apart) with or without concomitant HBeAg and HBV DNA ≥ 2000 IU/ml (the immune reactive phase and the HBeAg negative CHB phase). This condition is characterized by chronic necroinflammatory liver disease (elevated ALT and histological lesions in liver biopsy) related with persistent viral replication. Chronic hepatitis B can be subdivided into HBe-positive chronic hepatitis B and HBe-negative chronic hepatitis B. Hepatitis B e-negative chronic hepatitis B is the most common, representing nowadays about 70 to 80% of chronic hepatitis[16]. Therapy for HBV is indicated when HBV DNA levels are above 2000 IU/ml and/or the serum ALT levels are above the upper limit of normal and liver biopsy shows moderate to severe active necroinflammation and/or fibrosis.

Table I. Interpretation of hepatitis B virus serology

Serology	Interpretation
HBsAg – Anti-HBc – Anti-HBs –	Susceptible for HBV infection
HBsAg – Anti-HBc + Anti-HBs +	Past HBV infection
HBsAg – Anti-HBc + Anti-HBs –	Past HBV infection with undetectable levels of anti-HBs (more rarely, false positive anti-HBc, resolving acute infection or chronic HBV infection with undetectable levels of HBsAg)
HBsAg – Anti-HBc – Anti-HBs +	Immunization to HBV infection due to vaccination
HBsAg + Anti-HBc + / IgM anti-HBc + Anti-HBs –	Acute HBV infection (could also be a chronic infection/reactivation)
HBsAg + Anti-HBc + / IgM anti-HBc – Anti-HBs –	Chronic HBV infection

HBV, hepatitis B virus

- *inactive HBsAg carrier* is defined as the presence of HBsAg without HBeAg, normal aminotransferases and low viral load (<2000 IU/ml). These patients have persistent liver HBV infection without significant ongoing necroinflammatory disease (they have HBV "infection" without «hepatitis»). There is no indication for therapy in this group but they may be candidates for prophylaxis of HBV reactivation.
- *"resolved" hepatitis B* (the HBsAg-negative phase described above) is characterized by previous history of acute or chronic hepatitis B or the presence of anti-HBc (with or without anti-HBs). HBV DNA is usually undetectable in the serum, but may be detectable in hepatocytes. It is considered as potential occult hepatitis B infection (OBI). These concepts are outlined in Table II.

Hepatitis B infection and immunosuppressive therapy

The mechanism of HBV reactivation

The immunosuppressive schemes used in several diseases and in the transplantation field may influence HBV infection, accelerating the course of liver disease or reactivating it[17]. In most situations, reactivation of hepatitis B leads to an asymptomatic flare, but cases of decompensated liver disease, fulminant hepatitis and death have been described[12,18]. Liver damage in HBV reactivation occurs in two main occasions (Figure 1): massive viral replication during immunosuppression or in the immune restoration phase, immediately after the withdrawal of immunosuppression, which is characterized by an enhanced host immune response against HBV infected hepatocytes. This latter mechanism is the most implicated in liver damage, which can vary from a mild hepatitis to hepatic failure and death.

The rate of reactivation is higher in the context of hemato-oncological diseases (14 to 70%)[18,19]. HBV reaction can also occur in patients receiving chemotherapy for solid organs[20], and this complication can become more frequent due to the increasingly aggressive immunosuppressive regimens.

Severe cases of hepatitis flares have been described during treatment with anti-tumor necrosis factor (anti-TNF) agents in patients with rheumatoid arthritis[21,22] and inflammatory bowel disease (IBD)[23,24] with chronic HBV infection. With the widespread use of this class of drugs, more cases

Table II. Definition and diagnostic criteria of chronic hepatitis B, inactive HBsAg carrier state and resolved hepatitis B infection/occult B infection

	Chronic hepatitis B	Inactive carrier	"Resolved" hepatitis B (anti-HBc positive)
HBsAg	+	+	–
HBeAg	+/–	–	–
anti-HBs	–	–	+/–
anti-HBc	+	+	+
ALT	Persistent or intermittent increase	Persistently normal	Persistently normal
HBV DNA serum	+ (≥ 2000 IU/ml)	+ (< 2000 IU/ml)	–/+ (< 200 IU/ml)
HBV DNA tissue	+	+	+/–
Liver injury (necroinflammation)	Yes (>90%)	No (>90%)	No

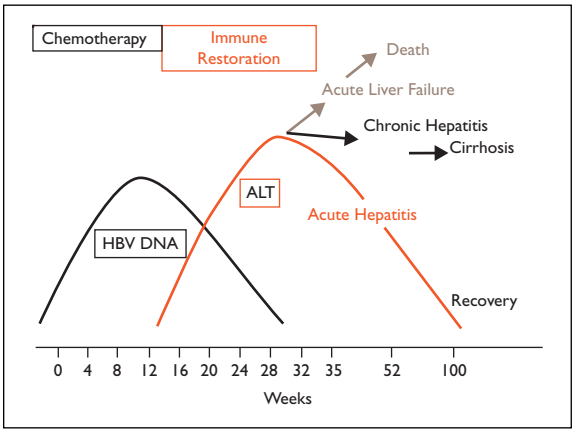

Figure 1. Hepatitis B reactivation and immunosuppressive therapy

of reactivation of HBV infection in inactive HBsAg carriers[25] and also in individuals with occult infection[26] have been reported. The long term follow-up of HBsAg negative/anti-HBc positive patients treated with anti TNF suggests that the reactivation rate is low. In fact, in a cohort of 72 patients followed for 43.5 ± 21.3 months no reactivation has occurred[27]. The issue of HBV reactivation has been included in review articles and consensus on the management of IBD patients[28,29]. The evidence seems to support that if HBV infection is properly diagnosed and treatment or prophylaxis is adequately begun the use of anti-TNF in hepatitis B patients is safe[30-32].

Other biological therapies, particularly rituximab (anti-CD20)[12,33-35] and alemtuzumab (anti-CD52)[36] have been involved in cases of HBV reactivation of HBsAg positive individuals and of HBsAg negative/anti-HBc positive patients with hemato-oncologic diseases. The risk of HBV reactivation with rituximab is higher when it is used in combination with chemotherapy, but it can occur with rituximab alone[35]. Reactivation of HBV seems to be less frequent in rheumatic patients treated with rituximab but some cases have been reported[37].

There are no reported cases of HBV reactivation in the context of the use of abatacept, anakinra and tocilizumab.

Apart from the use of biologics attention should be also paid to the use of other immunossuppressors for rheumatic diseases treatment. Of particular relevance is the use of moderate to high dose of corticoids for systemic lupus erythematosus management which have been clearly associated with HBV reactivation[38]. In addition, treatment of rheumatoid arthritis with low dose methotrexate (MTX) has been associated with fatal HBV reactivation in HBsAg negative/anti-HBc positive patients and the immunological reconstruction after MTX withdrawal has been also associated with fatal HBV reactivation[39-42].

Beyond the risk of a serious hepatic event, HBV reactivation associated with immunosuppression has a negative impact on their disease, delaying or hindering treatments that would be needed for remission induction or maintenance, with a significant impact on social and familiar aspects and in the quality of life of these patients.

There are some trials, including two randomized trials, showing that prophylactic therapy with lamivudine can reduce the rate of viral reactivation and mortality[43-45]. However, in the field of rheumatology, there are no national or international recommendations for the prophylaxis of HBV

reactivation, despite some previous discussions published in the context of case reports and reviews [21-28,46].

Who should be screened for HBV infection?

There is no consensus on which patients should be screened before the institution of an immunosuppressive therapy. There are two main strategies: screening patients considered at high risk for HBV infection or universal screening. The European Association for the Study of the Liver (EASL) guidelines[15], recommend universal screening of all candidates for immunosuppressive therapy. Given the absence of risk factors in many patients with HBV infection, the risk of HBV reactivation and the possibility of adequate prevention, we defend that screening should be universal. Thus, and referring to patients with rheumatic disease, all patients who will start or are assumed to require immunosuppressive therapy should be screened for HBV infection.

How to screen?

The screening for HBV chronic infection should be done with the determination of HBsAg, anti-HBc and anti-HBs. It is further recommended that patients with negative serological tests (HBsAg, anti-HBs and anti-HBc all negative) should be vaccinated as soon as possible, preferably with a rapid scheme, consisting of four doses at 0, 1, 2 and 12 months. The patients with positive HBsAg should be evaluated for viral load (HBV DNA by Real Time PCR)[47].

In vaccinated population, anti-HBs titles should be evaluated.

The difference between HBV therapy, prophylaxis and monitoring

The term *therapy* is reserved for treatment of patients with liver damage (chronic hepatitis B).

The term *prophylaxis* is used to characterize the use of antiviral agents in order to prevent viral reactivation. Prophylaxis can be performed on all individuals at risk (universal prophylaxis) or initiated only if evidence of reactivation, consisting in increased level of HBV DNA and/or seroreversion of HBsAg (i.e. HBsAg negative individuals that become positive) and hepatitis flare (targeted prophylaxis).

Monitoring is done by testing HBV DNA and aminotransferases periodically, with some authors suggesting a three to six months interval[7,46]. It was demonstrated that the increase of HBV DNA occurs early in the natural history of reactivation, preceding the aminotransferases flare[48,49]. If monitoring is the strategy, prophylaxis or therapy for HBV should be initiated as soon as there is increase in viral load.

Which rheumatic patients should start therapy and/or prophylaxis of HBV reactivation?

Reactivation of HBV depends fundamentally on two issues: phase of infection (active, inactive or occult B infection) and type of immunosuppression.

- *Chronic hepatitis B infection (HBsAg positive, HBV DNA³ 2000 IU/ml, increased or normal ALT, necroinflammation and fibrosis on liver biopsy).* This group of patients should start antiviral therapy for hepatitis B, whether performing or not immunosuppressive therapy [7,14,15]. Immunosuppressive therapy in patients with chronic hepatitis B under antiviral therapy is safe[50].
- *Inactive HBsAg carriers (HBsAg positive, HBV DNA <2000 IU/ml, normal ALT)*
  In these patients, there is a risk of HBV reactivation, which is related with the type of immunosuppression used. The use of steroids in medium or high dose (> 7.5 mg / day for long periods), anti-TNF drugs, rituximab, cyclophosphamide, methotrexate, leflunomide, calcineu-

Table III. Treatment strategies according to HBV stage

HBsAg Positive	
Chronic hepatitis B	Antiviral therapy (entecavir or tenofovir)
Inactive HBsAg carrier state	High risk therapy† Prophylaxis (entecavir, tenofovir, lamivudine*)
(HBV DNA > 2000 IU/ml)	Low risk therapy‡ Monitoring
HBsAg negative, Anti-HBc positive, (± anti-HBs)	High risk therapy† Monitoring

†glucocorticoids > 7.5 mg/day for long periods, anti-TNF, rituximab, cyclophosphamide, methotrexate, leflunomide, calcineurin antagonists, mycophenolate mofetil and azathioprine
‡ glucocorticoids <7.5 mg / day, sulphasalazine, hydroxychloroquine and gold compounds
*in very selected cases, with low or undetectable HBV DNA and immunosuppressive therapy expected for short period (less than 12 months)

Table IV. Stategies for hepatitis B treatment, prophylaxis and monitoring

Antiviral therapy	Entecavir	0,5 mg once daily Adverse effects (very rare): headache, nausea, fatigue,
	Tenofovir	300 mg once daily Adverse effects (<1%): renal tubular dysfunction proximal, osteoporosis, diarrhea, nausea, vomiting, skin rash Needs monitorization of serum phosphate, renal function
Prophylaxis	Same as for therapy	
	Lamivudine	100 mg once daily (short period of therapy)
Monitoring	HBV DNA, ALT and HBsAg periodically (6/6 months)	

rin antagonists, mycophenolate mofetil and azathioprine is associated with high risk of reactivation (14 to 70%) and thus these patients should perform universal prophylaxis, regardless of viral load[25]. Patients receiving glucocorticoids <7.5 mg/day, sulphasalazine, hydroxychloroquine and gold compounds are considered at low risk for HBV reactivation[46] (Table III). In these patients we recommend monitoring of HBV DNA, ALT, AST and HBsAg every 6 months, starting prophylaxis/therapy in the case of HBV reactivation (HBV DNA ≥ 2000 IU/ml and/or seroreversion of HBsAg).

- *Occult hepatitis B virus infection*

The management of occult B hepatitis virus infection is still a controversial issue. There are not enough data in the literature on this subgroup of patients. In two recent papers, no evidence of HBV reactivation was found in rheumatic patients treated with anti-TNF therapy and resolved hepatitis B (anti-HBc positive) [27,30]. Prophylaxis in this setting is not recommended. It is suggested monitoring for HBV reactivation (mainly those submitted to highly immunosuppressive treatments).

This concepts and decision algorithm is schematized in Table III.

When to start and to stop prophylaxis?

Prophylaxis should be started 2 to 4 weeks before the beginning of immunosuppressive therapy. As already mentioned, the risk of HBV reactivation is greater after the withdrawal of immunosuppression (immune restoration period). Therefore, prophylaxis should be maintained for at least 6 to 12 months after the suspension of immunosuppressants[14,15].

Which drugs to use?

Drugs with anti-HBV activity are based primarily on two groups: nucleoside/nucleotide analogues (NA) and pegylated interferons.

Pegylated interferons (alpha-2b or Pegintron® and alpha-2a or Pégasys®) have not only antiviral but also immunomodulador effects and may lead to acute hepatitis flares. They should not be used in this context.

The nucleoside/nucleotide drugs (NA) are orally administered (one pill a day), well tolerated and safe. There are several NA approved for the therapy of chronic hepatitis B: lamivudine and adefovir, which are first generation drugs having high levels

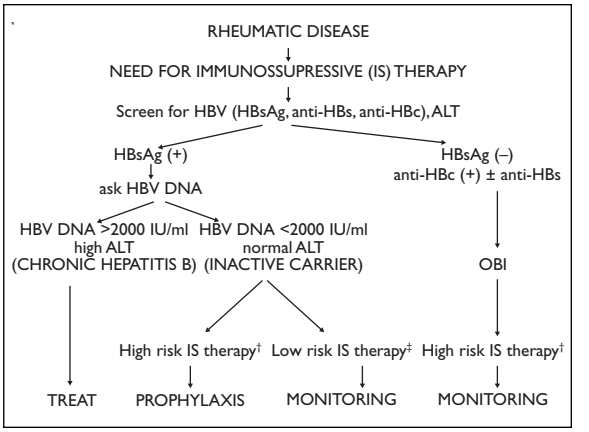

Figure 11. Algorithm to manage HBV infected patients undergoing immunosuppressive therapy for rheumatic diseases

*OBI – Occult B Infection; † glucocorticoids > 7.5 mg / day for long periods, anti-TNF, rituximab, cyclophosphamide, methotrexate, leflunomide, calcineurin antagonists, mycophenolate mofetil and azathioprine
‡ glucocorticoids <7.5 mg / day, sulphasalazine, hydroxychloroquine and gold compounds

of resistence[51], and entecavir and tenofovir, with high potency and low resistance profile[52]. Lamivudine is an inexpensive drug, but due to its low genetic barrier, with rates of resistance as high as 20% after one year and up to 75% at five years, it is no longer recommended as first line treatment of HBV. However, most studies of prophylaxis of HBV reactivation in patients undergoing immunosuppression are with lamivudine[43-45]. This drug can be a valid option in selected cases, like prophylaxis in HBsAg negative/anti-HBc positive during short term immunossupression, such as the case of hematologic or oncologic disorders. Nevertheless, in patients with higher viral loads (HBV DNA above 10^7 IU/ml) and in those in whom the duration of immunosuppressive therapy is expected to be held for more than a year, drugs with high potency and high genetic barrier (entecavir and tenofovir) should be considered as first line[15] (Table IV). They have excellent resistance profiles, with a rate of resistance of 1.2% at 6 years and 0% at 3 years respectively[53,54]. Entecavir and tenofovir have been successfully used as prophylactic agents to avoid HBV reactivation in patients under immunosuppressive therapy[55,56] or to treat hepatitis flares, in cases where prophylaxis was not done[57,58].

Conclusions and recommendations

1. Hepatitis B reactivation during immunosuppressive treatment can occur in any stage of HBV chronic infection; it can be severe and sometimes fatal due to liver failure. The withdrawal of the immunossupression is also a risk phase.
2. All patients who are candidates for immunosuppressive therapy should be screened for the status of HBV infection.
3. The screening should include ALT, HBsAg, anti-HBs and anti-HBc.
   a) In patients with HBsAg positivity, viral load (HBV-DNA) should be performed.
   b) In patients having HBsAg negative / anti-HBc positivity (± anti-HBs) occult hepatitis B infection is a possibility.
   c) Patients negative for all HBV markers should be vaccinated as soon as possible.
4. The management (whether prophylaxis or monitoring) of patients undergoing immunosuppressive with evidence of present or past HBV infection therapy is determined by the stage of HBV infection and the intensity of the immunosuppressive regimen.
5. HBsAg positive patients should be evaluated by a specialist in liver diseases to decide whether to start therapy (active carriers) or prophylaxis (inactive HBsAg carriers under high risk immunosuppressive therapies). Monitoring for HBV reactivation is indicated in inactive carriers under low risk immunosuppressive therapies and occult hepatitis B infection.
6. In HBsAg negative/anti-HBc positivity (± anti-HBs) patients, monitoring is indicated in cases of high risk immunosuppressive therapy.
7. Prophylaxis of HBV reactivation should be initiated 2 to 4 weeks before the beginning of immunosuppressive therapy and maintained 6 to 12 months after its suspension.
8. The drugs recommended for prophylaxis are nucleos(t)ide analogs like entecavir or tenofovir. Lamivudine can be used in selected cases (occult B hepatitis virus infection).
9. Monitoring HBV reactivation should be performed periodically (each 3 to 6 months) with the determination of aminotransferases and HBV DNA levels.

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BRUCELOSE OSTEO-ARTICULAR: UM RETRATO DOS ÚLTIMOS 10 ANOS

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Resumo

Objectivo: Caracterizar uma série de doentes com Brucelose Osteo-Articular (BO).
Material e Métodos: Estudo retrospectivo dos casos diagnosticados entre Janeiro/2000 e Dezembro/2009 nos Hospitais da Universidade de Coimbra (HUC).
Resultados: Foram internados 90 doentes com o diagnóstico de brucelose nos HUC, dos quais 44 (49%; 26 homens/18 mulheres; média de 49,5 anos) tinham complicações osteo-articulares. Em 25 (45%) doentes foi possível identificar um contexto epidemiológico positivo. O sintoma mais frequente foi a dor local (73%) seguido de poliatralgias e sintomas constitucionais. A proteína C-reactiva foi o marcador inflamatório mais frequentemente aumentado (82%). O teste de Rosa Bengala foi positivo em 42 doentes, e obteve-se um título de Wright superior a 1/160 em 28. Em 28 (64%) doentes foi isolado o agente etiológico, com 70% das hemoculturas positivas. O exame imagiológico mais utilizado foi a Ressonância Magnética (46%). A manifestação osteo-articular mais observada foi a espondilodiscite (57%) com envolvimento lombosagrado em 40%. Todos os doentes cumpriram antibioterapia. Um doente foi submetido a cirurgia para drenagem de abcesso. Os doentes tiveram uma duração média de internamento de 28,3 dias, com uma boa evolução em 60%, e uma evolução razoável em 20%, embora se tenha perdido o *follow-up* em 20%.
Conclusões: A brucelose é uma doença de declaração obrigatória ainda não erradicada em Portugal, mas com grande impacto a nível sócio-económico e de saúde pública. Por este motivo, torna-se relevante o conhecimento epidemiológico dos casos de brucelose permitindo uma intervenção e terapêutica precoces.

Palavras-Chave: Brucelose; Brucelose Osteo-Articular; Espondilodiscite.

Abstract

Objectives: Characterize Osteoarticular Brucellosis in the University Hospital of Coimbra (HUC) in the past decade.
Material and Methods: A retrospective study of the cases diagnosed between January/2000 and December/2009 in the HUC.
Results: Ninety patients were admitted with the diagnosis of brucellosis in our hospital, of whom 44 (49%; 18 men; 26 women, mean 49.5 years) had osteoarticular complications. Twenty-five (45%) patients had a positive epidemiological context. The most frequent clinical manifestation was local pain (73%) followed by polyarthralgias and constitutional symptoms. The C-reactive protein was the inflammatory marker most often increased (82%). The Rose Bengala test was positive in 42 patients, and a Wright's sero-aglutination above than 1/160 was detected in 28 patients. An etiologic agent was isolated in 28 (64%) patients, with 70% of positive blood cultures. The imaging procedure of choice was magnetic resonance imaging (MRI) (46%). The osteo-articular manifestation most frequent was spondylodiscitis (57%) with a lumbosacral involvement in 40%. All patients completed antibiotic therapy. One patient underwent surgery to drain the abscess. Patients had an average length of admission of 28.3 days, with a good outcome in 60%, and a reasonable outcome in 20%, despite 20% of the patients lost follow-up.
Conclusions: Brucellosis is a disease of obligatory declaration not eradicated in Portugal, with a great impact on socio-economic and public health. So, this epidemiological knowledge of brucellosis cases, allows an early intervention and therapy.

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Keywords: Brucellosis; Osteoarticular Brucellosis; Spondylodiscitis.

Introdução

A brucelose é uma zoonose causada por um cocobacilo intracelular do género *Brucella*. As espécies patogénicas para a espécie humana são quatro: *B. melitensis, B. abortus, B. suis* e *B. canis*. A brucelose é considerada típica dos países da bacia do Mediterrâneo, sendo endémica em Portugal. A transmissão ocorre por manipulação de animais infectados, bem como pela ingestão de leite ou derivados não pasteurizados. A doença pode evoluir segundo 3 formas: aguda (<8 semanas), crónica (>8 semanas) ou ondulante (períodos de remissão e exacerbações). A brucelose localizada ocorre durante a infecção aguda ou meses depois, e constitui uma causa de febre de origem indeterminada com diversas manifestações inespecíficas. Além da febre, podem ocorrer outros sintomas como hipersudorese, anorexia, astenia, fadiga, emagrecimento, depressão e artralgias.

O diagnóstico de certeza baseia-se no isolamento do agente por cultura, habitualmente no sangue. Contudo, é difícil e moroso (tempo de incubação entre 4 a 6 semanas). Deste modo, na maioria dos casos, o diagnóstico baseia-se em exames serológicos.

As complicações osteo-articulares são relevantes tendo em conta a sua alta prevalência e risco de sequelas. Em 20-40% pode ocorrer envolvimento osteo-articular, nomeadamente com artrite periférica, sacro-ileíte e espondilodiscite[1]. A sacro-ileíte é frequentemente não destrutiva e uni ou bilateral[2]. A espondilodiscite ocorre predominantemente na coluna, mais frequentemente no segmento lombar. Atinge caracteristicamente e de forma precoce, a região anterior da face superior do corpo vertebral, evoluindo para lesões erosivas, com ou sem formação de abcessos paravertebrais e posterior fusão dos corpos vertebrais[3]. O espectro de lesões osteo-articulares inclui ainda tenossinovites e bursites[1,4].

Objectivos

Caracterizar a brucelose osteo-articular (BO) do ponto de vista epidemiológico, clínico e terapêutico.

Material e Métodos

O estudo retrospectivo dos casos de BO, consistiu na análise das seguintes variáveis: idade, sexo, sintomatologia predominante, tempo de evolução dos sintomas, alterações laboratoriais, agente etiológico isolado, produto biológico em que foi feito o isolamento, exames imagiológicos realizados, localização da lesão por imagem, tratamento efectuado e evolução. Para tal, foi efectuada uma pesquisa na base de dados dos doentes internados nos diferentes Serviços dos Hospitais da Universidade de Coimbra (HUC), entre Janeiro de 2000 e Dezembro de 2009, com a palavra-chave: *Brucelose*. Posteriormente foram consultados os processos clínicos hospitalares dos respectivos doentes. Foram critérios de inclusão os doentes que apresentaram o diagnóstico de BO. Constituíram critérios de exclusão: brucelose aguda, outras formas de brucelose (como por exemplo, neurobrucelose, urogenital, abcessos abdominais, entre outras). O diagnóstico foi estabelecido com base em um dos seguintes critérios: a) isolamento de *Brucella* species no sangue ou em outro líquido biológico; b) quadro clínico compatível com brucelose (artralgias de características inflamatórias, dor em segmento de coluna e/ou défice neurológico *de novo* resultante de compressão radicular com achados imagiológicos por radiografia, cintigrama osteoarticular, TAC ou RMN) na presença de seroconversão ou demonstração de títulos elevados de anticorpos específicos por seroaglutinação[5].

A evolução foi classificada como: «Boa», se após a terapêutica houve resolução completa da clínica ou manteve apenas dor ligeira ou esporádica; «Razoável», quando, apesar de resolvido o quadro infeccioso, se manteve deformidade da coluna, défice neurológico e/ou dor que não ligeira; e «Má», se não houve resposta ao tratamento e/ou durante o tratamento[6].

Resultados

1. Dados demográficos

Na última década, foram diagnosticados 90 casos de brucelose, dos quais 44 (49%) correspondiam a BO, nos HUC. Em 2000 foi o ano em que se registaram mais novos casos (Figura 1). Vinte e seis (59%) eram do sexo masculino e 18 (41%) eram do sexo feminino. As idades estavam compreendidas entre os 16 e 83 anos, com uma média de 49,5 anos.

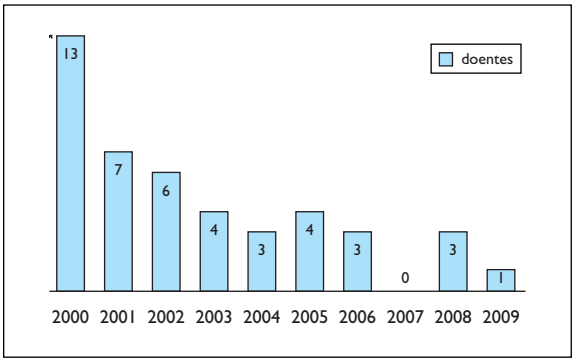

Figura 1. Distribuição do número de doentes com brucelose osteo-articular distribuídos por ano (n=44)

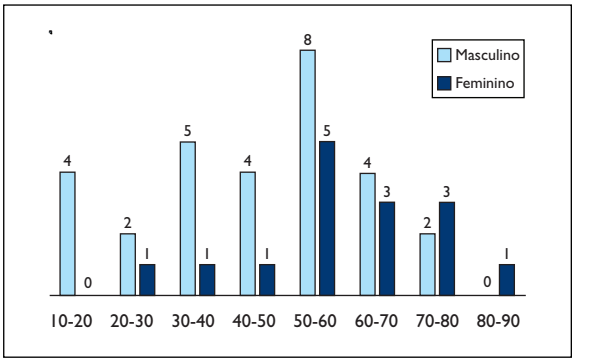

Figura 2. Número de casos em função da idade e do sexo (n=44)

Cerca de metade dos casos incluíam-se no grupo etário dos 50 aos 69 anos. A distribuição dos sexos em função da idade está representada no Figura 2.

2. Contexto Epidemiológico

Identificaram-se 25 (45%) doentes com contexto epidemiológico relevante: 13 pastores de gado ovino e/ou caprino, 4 trabalhadores em matadouro e 6 doentes com história de consumo de produtos não pasteurizados. Dois doentes tinham familiares com brucelose. Ocorreram 16 casos na região de Coimbra e da Guarda, 6 em Leiria, 5 em Castelo Branco e 1 em Viseu.

3. Manifestações Clínicas

Os sintomas mais frequentes foram a dor na coluna (73%), artralgias (35%) e os sintomas constitucionais (33%). O intervalo entre o início das queixas e o diagnóstico de BO foi em média 32 dias (mín. 2-máx. 109).

4. Alterações analíticas

Os parâmetros avaliados foram a velocidade de sedimentação na primeira hora (VS), que estava aumentada em 60% (VS média 68 mm/h) e a Proteína C-reactiva (PCR) que foi positiva (>0,5mg/dl) em 82% dos doentes (PCR média 7,5 mg/dl). Na nossa série não houve qualquer doente com leucocitose ou leucopenia.

O Teste de Wright teve um título superior a 1/160 em 28 (67%) das 42 amostras. O teste de Rosa Bengala foi positivo em todos os casos em que foi requisitado (Tabela I).

Tabela I. Exames bacteriológicos e serológicos

	Número de casos positivos/total (%)
Hemoculturas	25/36 (70)
Teste de Rosa Bengala	42/42 (100)
Teste de Wright >1/160	28/42 (67)

5. Manifestações osteo-articulares

As manifestações mais frequentes foram a espondilodiscite (57%) e as artralgias (35%) (Tabela II).

Tabela II. Complicações osteo-articulares

Local	Número de doentes (%)
Espondilodiscite	25 (57)
Cervical	1 (1)
Dorsal	3 (10)
Dorsolombar	2 (4)
Lombar	1 (2)
Lombo-sagrado	18 (40)
Sacro-ileite	8 (18)
Direita	4 (9)
Esquerda	2 (5)
Bilateral	2 (4)
Monoartrite	3 (6)
Punho	1 (2)
Anca	1 (2)
Joelho	1 (2)
Oligoartrite	7 (16)
Múltiplos locais*	3 (3)

*envolvimento simultâneo axial e periférico

Em terceiro lugar, encontra-se a sacro-ileíte (18%), mais frequente em jovens (entre os 16 e os 20 anos) do sexo masculino e na forma unilateral. Ocorreu ainda artrite (16%) predominantemente das pequenas articulações da mão, coxo-femoral, joelho e tibiotársica. A artrite séptica esteve presente em 3 (6%) doentes atingindo as articulações do punho, coxo-femoral e joelho.

6. Estudo imagiológico

Vinte (46%) doentes fizeram RMN e 12 (27%) TAC. Em 7 (16%) doentes identificaram-se abcessos, paravertebrais em 5 e epidurais em 2. Cerca de 2/3 dos doentes com espondilodiscite não teve envolvimento dos ligamentos vertebrais ou da porção posterior das vértebras. O aspecto radiológico na RMN mostra o corpo vertebral parcialmente homogéneo com hiposinal em T1 e hiperintensidade em T2. Nos casos avançados, poderá visualizar-se redução do espaço intervertebral com fibrose ocorrendo diminuição da intensidade em T2. No envolvimento paravertebral, geralmente observa-se edema de partes moles sem a presença de abscessos e com envolvimento da faceta vertebral.

Em um doente com espondilodiscite lombar a RMN mostrou destruição vertebral e compressão medular, semelhante aos achados de uma espondilodiscite de origem tuberculosa (Doença de Pott).

Os segmentos da coluna mais frequentemente envolvidos foram o lombosagrado e lombar, em 40% e 28% dos doentes respectivamente.

7. Diagnóstico etiológico

Em 28 (64%) doentes houve isolamento de agente etiológico em um ou mais produtos biológicos: sangue (25 doentes), líquido articular (2 doentes), pús do abcesso paravertebral (1 doente). Nos restantes doentes, o diagnóstico foi baseado na serologia positiva (por reacção de aglutinação de Wright superior a 1/160 ou teste de Bengala positivo).

8. Tratamento

Todos os 44 doentes com BO foram tratados com combinação de antibioterapia dupla ou tripla. Em 90% dos doentes foi eleito um tratamento baseado na antibioterapia dupla, tendo sido o esquema de eleição a combinação de doxiciclina (100mg 2id) com rifampicina (900mg id). Em 10% foi realizada antibioterapia tripla com doxiciclina (100mg 2id), rifampicina (900mg id) e estreptomicina (1g im id nos primeiros 14-21dias). A duração média do tratamento foi de 88,6 dias (mín. 32- máx. 365).

9. Evolução clínica

Vinte e seis (60%) doentes tiveram boa evolução e 9 (20%) doentes evolução razoável. Três destes nove doentes foram submetidos a cirurgia por instabilidade vertebral ou radiculopatia. Não ocorreu uma má evolução nos nossos doentes. Em 9 (20%) doentes o *follow-up* foi perdido.

Discussão

A brucelose é uma doença de declaração obrigatória, constituindo um importante problema de saúde pública, nomeadamente nos países mediterrânicos, permanecendo não erradicada em Portugal. Os autores apresentaram os casos diagnosticados na última década num Hospital Central, com uma grande área de influência. Estes dados epidemiológicos são particularmente importantes e úteis em Portugal, dada a escassez de séries publicadas sobre este tema. A principal limitação, e dado que se trata de um estudo retrospectivo, é a escassez de alguns dados clínicos, analíticos e imagiológicos.

Na última década ocorreu uma redução do número de casos de BO. A maior incidência da doença no sexo masculino está concordante com a literatura[7]. A idade e a distribuição por sexo encontrada neste estudo é provavelmente o reflexo de hábitos regionais, principalmente devido às práticas de criação de gado e trabalho em matadouros tornando os homens mais vulneráveis à brucelose. Verificou-se uma maior incidência em indivíduos com idades compreendidas entre os 50 e 69 anos, grupo etário que mantém o exercício de actividades rurais. O atraso de diagnóstico pode ser evitado através de uma anamnese completa, com investigação dirigida às prováveis fontes de contágio. É de particular importância compreender o modo de transmissão de brucelose uma vez que este conhecimento ajuda a aplicar medidas adequadas.

O quadro clínico de apresentação da brucelose nos doentes estudados foi semelhante às manifestações descritas noutros estudos[7-9]. A dor local foi o sintoma predominante, na maioria dos casos lombosagrada; menos frequentemente surgiram artralgias, sintomas constitucionais, hipersudorese, febre e ciatalgia. Alguns estudos mostram um predomínio de artrite periférica, possivelmente porque incluíram uma elevada proporção de doentes com idade inferior a 14 anos, em que a prevalência de artrite periférica é bem conhecida[10]. O

quadro inespecífico observado na maioria dos doentes com BO condiciona dificuldades e atrasos no diagnóstico prolongando o tempo entre o início das queixas e o diagnóstico. A duração da brucelose sem tratamento adequado tem sido relacionada directamente com elevada taxa de complicações e evolução desfavorável[11].

Como descrito noutros trabalhos, foi muito frequente a elevação da VS e da PCR[9]. O Teste de Wright consiste na prova laboratorial específica mais usada para a confirmação do diagnóstico. É geralmente aceite que um título superior a 1/160, na presença de clínica compatível confirma o diagnóstico. Recentemente, é possível usar também o teste ELISA, que apresenta uma maior sensibilidade e especificidade em relação ao Teste de Wright. Um estudo comparativo entre os testes serológicos clássicos e o teste ELISA incluindo 75 doentes com brucelose, constatou que cinco doentes com teste ELISA positivo tinham um teste de Wright negativo[12]. Outros estudos mostraram que o Teste de Wright e o ELISA são semelhantes em termos de diagnóstico serológico[13].

A hemocultura foi positiva em 70%, valor semelhante ao encontrado na literatura (50 a 90%)[14]. Realça-se a necessidade de informar o laboratório sobre o agente suspeito, uma vez que o crescimento da *Brucella* é lento. Nos casos sem isolamento de agente etiológico, as alterações serológicas e imagiológicas sugestivas de BO foram consideradas diagnósticas.

A prevalência de espondilodiscite é semelhante à encontrada em outros trabalhos[8,15]. A presença de abcessos paravertebrais ou epidurais encontra-se elevada em relação ao número apresentado por outras séries, o que provavelmente está relacionado com a acurácia dos meios de diagnóstico e a utilização da RMN, um meio de diagnóstico com elevada sensibilidade no diagnóstico precoce de espondilodiscite[15,16]. Na nossa série, a focalização predominante foi a coluna lombo-sagrada e dorsal, à semelhança de outros trabalhos[17-20].

A terapêutica foi exclusivamente médica, exceptuando três casos cirúrgicos. O tratamento médico da BO é ainda controverso, quer quanto à escolha dos antibióticos, quer à duração do tratamento. Os doentes com espondilodiscite brucélica apresentam melhor resposta à doxiciclina-estreptomicina ou a um regime triplo (doxiciclina-estreptomicina-rifampicina) do que à doxiciclina-rifampicina[21]. Num estudo prospectivo de 90 doentes com BO tratados durante mais de 5 meses as taxas de recidiva foram inferiores do que às dos tratados durante 6 semanas[22]. Os doentes com focalização osteo-articular beneficiam de uma terapia prolongada e a duração recomendada é no mínimo 3 meses[23].

Na nossa série, a maioria dos doentes apresentou uma boa evolução clínica. Os 9 doentes com evolução razoável foram doentes com espondilodiscite, que apesar da infecção resolvida, mantiveram lombalgia intensa e/ou défice neurológico associado.

Conclusões

A nossa série de 44 doentes descreve a realidade dos HUC em termos de brucelose com envolvimento osteo-articular, reflectindo quer as dificuldades de diagnóstico, quer a apresentação clínica inespecífica.

Deste modo, a BO deve ser incluída no diagnóstico diferencial de um doente com queixas osteo-articulares, especialmente com artralgias ou sintomas de osteomielite ou espondilodiscite. O índice de suspeição deverá ser elevado em regiões onde a doença é endémica.

A RMN é o exame complementar de diagnóstico fundamental para o estudo de envolvimento osteoarticular e estruturas associadas. A terapêutica médica foi instituída de acordo com as normas internacionais da OMS. A evolução foi favorável (boa ou razoável) na maioria dos doentes. Portanto, nos casos de espondilodiscite é importante intensificar medidas terapêuticas e manter um controlo rigoroso para detectar o mais precoce possível e corrigir eventuais compressões medulares ou radiculares.

Finalmente, referimos ainda o facto de se tratar de uma doença de declaração obrigatória sendo muito importante o registo de todos os casos diagnosticados para que haja um verdadeiro conhecimento da realidade.

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CURVAS OSTEODENSITOMÉTRICAS NUMA POPULAÇÃO DE MULHERES

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Resumo

Objectivo: Construir as curvas osteodensitométricas de referência para diferentes localizações anatómicas para uma população de mulheres.
Participantes e Métodos: Participaram no estudo 573 mulheres, de etnia caucasóide e residentes na região do Porto. A avaliação densitométrica foi realizada utilizando o método de absorciometria bifotónica com Rx (DEXA) em densitómetro Hologic® QDR 1500. A densidade mineral óssea (DMO) foi medida na coluna lombar e fémur proximal esquerdo e expressa em g/cm^2. A partir dos resultados obtidos por densitometria determinámos a DMO média, por grupo etário, e a média de DMO da adulta jovem (20-39 anos) para cálculo dos *T-scores* para as diferentes localizações com o objectivo de proceder à construção da base de referência. Na construção das curvas de referência recorremos a regressões polinomiais da DMO na idade.
Resultados: O pico de densidade óssea foi encontrado entre os 20 e os 29 anos para a coluna lombar e triângulo de Ward, e entre os 30 e os 39 anos nas restantes localizações estudadas. A DMO média (desvio-padrão) máxima ascendeu a 1,011 (0,124), na coluna lombar; 0,819 (0,118), a nível do colo do fémur; 0,708 (0,084), na região trocantérica; 1,115 (0,113), na região intertrocantérica; 0,783 (0,168), no triângulo de Ward e 0,951 (0,101), no fémur total.
Conclusão: Na amostra o pico de densidade óssea encontrou-se para a coluna lombar e triângulo de Ward na faixa etária dos 20-29 anos e entre os 30--39 anos paras as restantes localizações estudadas. Os valores médios de DMO por grupo etário na amostra são menores que os valores de referência da base instalada.

Palavras-chave: Densidade mineral óssea; Absorciometria Bifotónica por RX; Osteoporose; Pico de Densidade Óssea.

Abstract

Aim: To define female bone osteodensitometric reference curves, for different anatomical sites, in a female population.
Participants and Methods: A cross-sectional study was performed involving 573 Caucasoid women living in Porto. Bone mineral density was measured using a Hologic® QDR 1500 dual X-ray absorciometry system. Bone mineral density was measured at lumbar spine and proximal left femur and expressed in g/cm^2.

Participants were submitted to a bone densitometry by DEXA technique, for the different sites under study. After the results obtained trough densitometry mean BMD was calculated to each age group. Additionally, mean BMD was calculated for young adults (20-39 years old) in order to determine *T-scores* to draw a reference base. To define reference curves, polynomial regressions of BMD on age were used.
Results: Peak bone mass was found between 20 and 29 years old for lumbar spine and Ward's triangle, and between 30 and 39 years old for the remaining sites under study. Maximum mean (standard deviation) BMD was 1,011 (0,124) for lumbar spine; 0,819 (0,118) for femur neck; 0,708 (0,084) for the trochanteric region; 1,115 (0,113) for intertrochanteric region; 0,783 (0,168) for Ward's triangle and 0,951 (0,101) for total femur.
Conclusion: Bone mass peak was achieved in lumbar spine and in Ward's triangle, between 20 and 29 years old, and between 30 and 39 years for the other studied loci. The sample BMD peak values are lower than the machine reference values.

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Keywords: Bone Mineral Density; Dual Energy X-ray Absorptiometry; Osteoporosis; Peak Bone Mass.

Introdução

A osteoporose é uma doença de etiologia multifactorial que se caracteriza pela diminuição da massa óssea e pela deterioração da microarquitectura do tecido ósseo, aumentando o risco de fractura[1]. Face ao actual envelhecimento demográfico e ao aumento da esperança média de vida, as fracturas osteoporóticas afectam um grande segmento da população apontando as projecções, a nível mundial, para o agravamento da situação com o inerente acréscimo de custos, quer directos quer indirectos[2,3].

O diagnóstico da osteoporose baseia-se na medição da densidade mineral óssea (DMO), que pode ser efectuada através de diferentes técnicas de densitometria óssea, e na subsequente classificação de acordo com a definição operacional de osteoporose da Organização Mundial de Saúde (OMS)[4]. A definição densitométrica de osteoporose representa a distância, em unidades de desvio-padrão, ao valor médio de DMO determinado numa população padrão de mulheres adultas jovens e saudáveis, de etnia caucasóide medida por absorciometria bifotónica com radiação X (DEXA)[5].

É conhecida a variabilidade da DMO entre diferentes populações caucasóides, o que sugere a existência de diferenças nos valores de pico de densidade óssea, bem como nos padrões de perda de massa óssea[1,5-7]. O estabelecimento de curvas osteodensitométricas para mulheres portuguesas é de grande importância, dado que permite obter informações sobre a nossa realidade concreta, sendo então possível estabelecer estratégias e prioridades no controlo da doença.

O objectivo deste trabalho foi construir curvas densitométricas de referência para diferentes localizações anatómicas para uma população de mulheres portuguesas.

Participantes e Métodos

A população alvo deste estudo foi constituída por mulheres adultas de idade igual ou superior a 18 anos residentes na cidade do Porto, avaliadas entre 1999 e 2003 – o estudo EPIPorto, previamente descrito noutros trabalhos[8,9]. Para o contacto telefónico utilizou-se um método de marcação de dígitos de telefone ao acaso ("*random digit dialling*"), fixando os indicativos telefónicos da área de residência (três primeiros dígitos) e fazendo uma aleatorização simples processada por computador dos quatro últimos algarismos. A proporção de participação foi de 70%. A informação analisada neste estudo diz respeito aos indivíduos do sexo feminino com idade igual ou superior a 20 anos. Foram excluídas as participantes que estivessem grávidas aquando da avaliação.

Para todas as participantes foi recolhida informação, através da aplicação de um questionário, sobre aspectos sócio-demográficos, comportamentais, clínicos e ginecológicos. Consideraram-se menopáusicas as mulheres cuja ultima menstruação tinha ocorrido há 3 ou mais meses; todas as outras foram classificadas como pré-menopáusicas. Procedeu-se ainda à avaliação antropométrica (estatura e peso) e avaliação da DMO.

A avaliação densitométrica foi realizada utilizando o método de absorciometria bifotónica com RX (DEXA) em densitómetro Hologic® QDR 1500. Utilizou-se como população de referência a base fornecida pelo fabricante para mulheres jovens de etnia caucasóide norte-americana. A medição da densidade mineral óssea efectuou-se a nível da coluna lombar (L_1-L_4) em projecção postero-anterior e fémur proximal esquerdo, salvo em situações da existência de prótese local ou história prévia de fractura traumática. No fémur proximal foram avaliadas as seguintes regiões: colo do fémur, região trocantérica e inter-trocantérica, triângulo de Ward e fémur total. Os valores da densidade mineral óssea expressaram-se em g/cm^2. A reprodutibilidade do densitómetro foi avaliada recorrendo à utilização de um modelo antropomórfico de coluna lombar fornecido pelo fabricante. Este fantoma é constituído por hidroxiapatite trisulfato cuja densidade e área são equivalentes às da coluna lombar *in vivo*. O controlo de qualidade efectuou-se diariamente, antes da execução do primeiro exame do dia.

Considerou-se como população de referência para a distribuição da DMO as mulheres com menos de 40 anos de idade. Calculando a média e o desvio padrão desta distribuição, a cada mulher foi atribuído um valor de *T- score* igual à diferença entre o seu valor da DMO e a média em unidades de desvio padrão.

Na coluna lombar apenas foi possível avaliar a DMO em 567 mulheres porque as restantes, 2 mulheres no grupo etário dos 60-69 anos e 4 mulheres com idade igual ou superior a 70 anos, apresentavam indefinição dos corpos vertebrais ou erros relacionados com factores técnicos. Por razões técnicas foram eliminados valores de DMO ao nível do fémur proximal, existindo 572 medições a nível do colo do fémur e 571 para as restantes localizações.

Para comparar os valores médios máximos de DMO entre diferentes populações, utilizámos fórmulas de conversão entre equipamentos de DEXA para a coluna e para o colo do fémur, dado que os valores de DMO da amostra foram recolhidos num densitómetro QDR (Hologic®) e as tabelas osteodensitométricas de outros países são apresentadas em medições recolhidas em densitómetros DPX (Lunar®). As fórmulas de conversão utilizadas foram as seguintes:

$$\text{LunarDPXDMO}_{\text{coluna lombar}} = (1{,}074\ \text{Hologic® QDR DMO}_{\text{coluna lombar}}) + 0{,}054$$

$$\text{LunarDPXDMO}_{\text{colo fémur}} = (1{,}013 \leftrightarrow \text{Hologic® QDR DMO}_{\text{colo fémur}}) + 0{,}142$$

Análise de dados

Na análise das características das mulheres estudadas segundo o grupo etário utilizou-se o teste do Qui-quadrado para variáveis categóricas e análise de variância para variáveis contínuas. Para descrever o padrão de variação da DMO nas várias regiões segundo o grupo etário utilizou-se a análise de variância e contrastes de médias em grupos etários adjacentes. Foram realizadas regressões polinomiais da DMO na idade para estabelecer curvas normais padrão para as diferentes localizações. Para seleccionar o modelo polinomial que melhor ajustava aos dados utilizaram-se os coeficientes de polinómios ortogonais, evitando assim a extrema correlação entre as variáveis independentes (multicolinaridade). Com base no modelo de regressão mais adequado foram representadas graficamente as curvas padrão, acompanhadas do desvio padrão da DMO em cada região. Para testar os pressupostos nos modelos aplicados foi usado o teste de Kolmogorov-Smirnov (distribuição normal nas variáveis e/ou resíduos) e o teste de Levene para a homogeneidade de variâncias.

Os dados foram tratados utilizando o programa BMDP *Statistical Software* (1992).

Resultados

Características das mulheres estudadas segundo o grupo etário

A amostra foi constituída por 573 mulheres, com idade compreendida entre os 20 e os 86 anos, sendo a média (desvio-padrão) da idade de 53,9 (13,2) anos. A Tabela I representa a distribuição do peso, altura e idade da menopausa das mulheres estudadas, segundo o grupo etário.

As participantes no estudo apresentavam uma estatura média (desvio-padrão) de 155,4 (6,1) cm. Globalmente, a estatura diminuiu significativamente quando a idade aumentou. A partir da análise de comparações múltiplas verificámos que as mulheres mais novas tinham uma estatura superior à das mulheres entre os 40 e 59 anos de idade e estas últimas uma estatura superior à das mulheres com 60 e mais anos. O peso das mulheres variou entre 37,3 Kg e 117,1 Kg, sendo a média de 66,1 (12,3) Kg, aumentando até aos 59 anos e diminuindo nos grupos etários seguintes. As mulheres mais novas tinham um peso significativamente mais baixo que as mulheres no grupo etário dos 50-59 anos.

A menopausa ocorreu em média aos 47,6 (5,6) anos.

Tabela I. Distribuição do peso, altura e idade da menopausa por grupo etário (Médias ± desvios-padrão)

	Grupo etário						
Idade	**20-39**	**40-49**	**50-59**	**60-69**	**≥70**	**Total**	**p**
N° Mulheres	73 (12,6%)	141 (24,6%)	155 (27,1%)	133 (23,2%)	71 (12,4%)	575	–
Estatura	159,4 (6,7)	156,1 (5,6%)	156,2 (5,6)	153,4 (5,2)	151,8 (6,2)	155,4 (6,1)	0,001
Peso Kg	63,0 (10,8)	65,3 (11,1)	68,6 (12,9)	66,3 (12,8)	65,3 (12,7)	66,1 (12,3)	0,050
Idade da menopausa	–	42,8 (4,8)	48,1 (4,5)	47,9 (6,4)	48,9 (5,4)	47,6 (5,6)	0,001

Tabela II. Distribuição da densidade mineral óssea média (desvio-padrão) em g/cm² na região da coluna e do fémur proximal por grupo etário

Idade (anos)	n	Região Coluna L1-L4 n=567	Cólo fémur n=572	Trocanter n=571	Intertrocantérica n=571	Triângulo Ward n=571	Fémur Total n=571
20-29	28	**1,011**	0,814	0,699	1,086	**0,783**	0,931
		(0,124)	(0,132)	(0,101)	(0,159)	(0,168)	(0,135)
30-39	45	1,006	**0,819**	**0,708**	**1,115**	0,712	**0,951**
		(0,102)	(0,118)	(0,084)	(0,113)	(0,114)	(0,101)
40-49	141	0,981	0,766	0,692[c]	1,097[c]	0,644[c]	0,926[c]
		(0,116)	(0,099)	(0,088)	(0,148)	(0,124)	(0,114)
50-59	155	0,904	0,724	0,646	1,038	0,568	0,874
		(0,160)	(0,117)	(0,104)	(0,165)	(0,133)	(0,132)
60-69	133	0,822[a]	0,657[c]	0,603[c]	0,981[c]	0,475[c]	0,815[c]
		(0,153)	(0,103)	(0,099)	(0,158)	(0,120)	(0,126)
≥70	71	0,826[b]	0,632	0,568	0,925	0,437	0,773
		(0,152)	(0,095)	(0,086)	(0,133)	(0,102)	(0,107)
Total	573	567	572	571	571	571	571

Valores: (a) 2 mulheres não incluídas; (b) 4 mulheres não incluídas; (c) 1 mulher não incluída)
] Grupos homogéneos (5 contrastes ortogonais); traço carregado no pico de densidade óssea nas diferentes localizações.

Distribuição da Densidade Mineral Óssea por grupo etário

Na nossa amostra os valores da DMO apresentaram uma distribuição normal em todas as localizações anatómicas.

Na Tabela II descreve-se sumariamente a distribuição da DMO na região da coluna e do fémur proximal por grupo etário. O valor médio mais elevado de DMO a nível da coluna lombar (1,011 g/ /cm²) foi observado no grupo etário dos 20 a 29 anos, correspondendo assim ao pico de densidade óssea para esta localização. A nível do fémur proximal, os valores médios máximos de DMO para as diferentes regiões foram maioritariamente atingidos no grupo etário dos 30 aos 39 anos, respectivamente, colo do fémur (0,819 g/cm²), região trocantérica (0,708 g/cm²), região inter-trocantérica (1,115 g/cm²) e fémur total (0,951 g/cm²), exceptuando-se a região do triângulo de Ward em que o valor máximo de DMO foi encontrado no escalão etário dos 20 aos 29 anos (0,783 g/cm²). Verificou-se que, para todas as regiões avaliadas, a partir dos 40 anos, os valores médios de DMO diminuíram, com excepção para o valor obtido na coluna lombar para as mulheres com idade igual ou superior a 70 anos, sendo este superior ao das mulheres com idades compreendidas entre os 60 e 69 anos.

Na comparação da DMO por grupo etário, foram encontrados quatro padrões distintos: (a) região da coluna L1-L4, (b) colo do fémur, (c) região trocantérica, intertrocantérica, fémur total, e (d) triângulo de Ward. A DMO na coluna L1-L4 diminuiu significativamente no grupo etário 50-59 anos (p<0,001), sendo esta redução igualmente significativa (p<0,001) nos 60-69 anos.

No colo do fémur a redução foi mais precoce, no grupo etário dos 40-49 anos (p <0,01 para a comparação com a classe 20-39 anos), verificando-se essas reduções até aos 60-69 anos (p <0,001 para a comparação com a classe 20-39 anos). Nas regiões trocantérica, intertrocantérica e no fémur total o padrão foi semelhante, existindo uma redução significativa aos 50-59 anos (p <0,001), seguida de sucessivas reduções até ao grupo etário mais velho (p <0,05). Finalmente, na região do triângulo de Ward, a mais sensível, existiram sucessivas reduções em todos os grupos etários (p <0,05).

Curvas normais para as diferentes localizações

Na coluna lombar e no colo do fémur o polinómio de grau 3 forneceu um melhor ajuste, enquanto nas regiões trocantérica, intertrocantérica e no fémur total foi o polinómio de grau 2 e no triângulo de Ward o modelo linear simples. Na Tabela III

Tabela III. Equações de regressão e coeficiente de determinação para as diferentes regiões anatómicas

Região	Equação de regressão	R^2 (%)
Coluna Lombar	DMO = 0,409 – 4,53 × 10^{-2} × Idade – 1,01 × 10^{-3} × Idade + 6,41 × 10^{-6} × Idade^3 (2,1)* (3,7) (4,1) (4,0)	21,9
Cólo do fémur	DMO = 0,517 – 2,40 × 10^{-2} × Idade – 5,68 × 10^{-4} × Idade^2 + 3,57 × 10^{-6} × Idade^3 (3,5) (2,6) (3,0) (2,9)	24,7
Trocanter	DMO = 0,692 – 2,16 × 10^{-3} × Idade – 5,31 × 10^{-5} × Idade^2 (14,1) (1,1) (-2,9)	19,4
Intertrocantérica	DMO = 1,05 – 4,89 × 10^{-3} × Idade – 8,96 × 10^{-5} × Idade^2 (13,4) (1,6) (-3,1)	14,8
Triângulo de Ward	DMO = 0,969 – 7,39 × 10^{-3} × Idade (44,6) (-18,8)	38,5
Fémur total	DMO = 9,932 – 2,62 × 10^{-3} × Idade – 6,59 × 10^{-5} × Idade^2 (14,9) (1,1) (-2,9)	19,1

*Valor da estatística t para o coeficiente

descrevem-se as equações estimadas para as diferentes regiões, o valor da estatística *t* para os parâmetros estimados e o coeficiente de determinação obtido para cada um dos modelos seleccionados.

Na Figura 1 de A a F estão representados graficamente os modelos da Tabela III conjuntamente com as linhas definindo a média da DMO ± 2 desvios-padrão.

Comparação entre o pico de densidade óssea da escala Hologic e o valor de pico de densidade óssea determinado a partir da amostra estudada

Comparando os resultados encontrados para as diferentes localizações em relação ao pico de densidade óssea (Tabela IV), podem avaliar-se as diferenças existentes para as várias regiões estudadas utilizando a base de referência Hologic® para mulheres jovens da população geral norte-americana de etnia caucasiana e a base construída a partir da amostra estudada.

A média em relação ao pico de densidade óssea para cada localização, como valor referido pelo fabricante, excedeu a média da escala definida a partir da amostra estudada em qualquer uma das localizações consideradas. Com efeito, a média do pico de densidade óssea fornecida pelo fabricante excedeu a que encontrámos em 0,036g/cm^2 (3,6%) na coluna, 0,076g/cm^2 (9,4%) no colo do fémur, 0,014g/cm^2 (2,0%) no trocanter, 0,033g/cm^2 (3,0%) na região inter-trocantérica, 0,013g/cm^2 (1,7%) no triângulo de Ward e 0,024g/cm^2 (2,5%) no fémur total.

Discussão

Na presente amostra de mulheres portuguesas avaliou-se a variação na densidade mineral óssea em função da idade, propondo-se curvas padrão osteodensitométricas para a população portuguesa. Este estudo apresenta como principal limitação ter sido realizado a partir de dados transversais. Desta forma, na interpretação dos resultados, é importante ter em conta que parte do efeito atribuído à idade poderá ter sido confundido por efeitos de coorte ou de período.

O pico de densidade óssea encontrou-se para a coluna lombar e triângulo de Ward no grupo etário 20-29 anos e no grupo etário 30-39 anos para as restantes localizações estudadas. Em todas as regiões analisadas os valores médios de DMO diminuíam sucessivamente a partir dos 40 anos, exceptuando-se os valores para a coluna lombar das mulheres com mais de 70 anos.

Foi possível comparar os valores médios da DMO na amostra estudada com os valores de referência (média e desvio padrão da DMO) para a população de Coimbra[10] e população espanhola[11], utilizando comparações múltiplas com um nível de significância ajustado. Em relação à DMO na região lombar não se encontraram valores significativamente diferentes entre a amostra do Porto e as amostras de Coimbra e da população espanhola. No entanto, no colo do fémur, a DMO média na amostra do Porto era significativamente mais baixa que nas outras duas amostras no grupo etário dos 60-69 anos, 0,657 comparado com 0,701 e

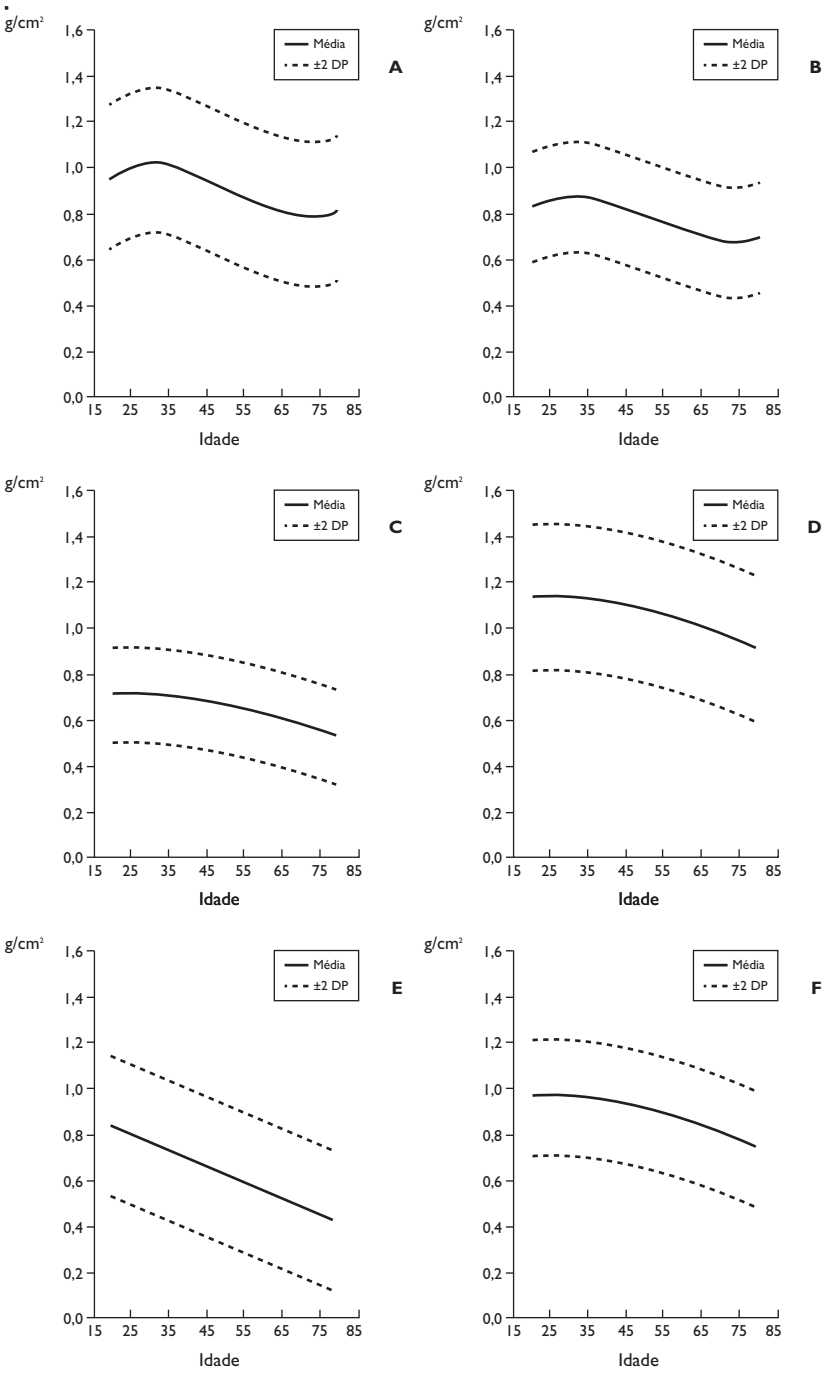

Figura 1. Valores padrão para a DMO nas regiões: A) coluna lombar, B) Colo do fémur, C) Trocantérica, D) Intertrocantérica, E) Triângulo de Ward e F) Fémur total

Tabela IV. Diferenças para pico de densidade óssea nas diferentes localizações estudadas entre a base de referência Hologic®* e a base construída a partir da amostra

	Hologic®*	Amostra	Diferença: Base Hologic®* e Amostra	Percentagem (%)
Coluna L1-L4	1,047	1,011	0,036	3,6%
Colo fémur	0,895	0,819	0,076	9,4%
Trocanter	0,722	0,708	0,014	2,0%
Intertrocantérica	1,148	1,115	0,033	3,0%
Triângulo Ward	0,796	0,783	0,013	1,7%
Fémur total	0,975	0,951	0,024	2,5%

*Base de dados Hologic® construída pelo fabricante a partir de uma amostra da população geral americana constituída por mulheres jovens de etnia caucasóide.

0,694 g/cm^2, respectivamente para as amostras de Coimbra e população espanhola. As diferenças entre as bases de referência analisadas podem tão só originar-se no facto dos critérios de inclusão/exclusão adoptados nos vários estudos serem diferentes. Enquanto no estudo espanhol foram estabelecidos critérios de exclusão (mulheres com fractura por queda; mulheres utilizando THS), no estudo do Porto isso não aconteceu. Para permitir a melhor comparabilidade dos resultados encontrados, calculamos novamente a média da DMO no colo do fémur para este grupo etário excluindo as mulheres com fracturas por queda, obtendo-se um valor médio (desvio-padrão) de 0,671 (0,104) g/cm^2, este já não significativamente diferente dos mencionados nas outras duas amostras.

Coluna Lombar

Na coluna lombar, verificámos um decréscimo da DMO à medida que aumentou a idade a partir dos 49 anos, resultado este que está de acordo com os anteriormente obtidos por outros investigadores noutros países[12,13]. O valor de DMO para o grupo etário 50-59 anos é inferior ao observado nos grupos etários precedentes. Provavelmente esta baixa significativa da DMO está relacionada com o incremento da perda de massa óssea que se verifica nos primeiros anos após a menopausa, que ocorreu na nossa amostra em média aos 47,6 anos.

Esta diferença não é tão marcada quando comparamos os valores de DMO nas mulheres do grupo etário 60-69 anos e com idade superior a 70 anos. Estes resultados são consistentes com a diminuição da velocidade de perda de massa óssea que se verifica nestas classes etárias, como tem sido sugerido por vários investigadores[14-16].

Contudo, podemos verificar que as mulheres acima dos 70 anos apresentam um valor de DMO ligeiramente mais elevado que o grupo etário precedente, podendo este aumento artificial dever-se à presença de calcificações degenerativas a nível da coluna lombar já descritas na população mais idosa[5,6,12,16,17].

Fémur Total

No fémur total, o pico de densidade óssea foi observado no grupo etário dos 30-39 anos, isto é, na década posterior à encontrada para a coluna lombar. No nosso estudo, observámos uma rápida perda de massa óssea nesta região, acima dos 50 anos, o que se encontra de acordo com estudos anteriores[16,18,19]. No entanto, outros investigadores sugerem uma diminuição linear da massa óssea desde a entrada na idade adulta[20,21]. Tal facto não se verifica na amostra estudada, observando-se que a diminuição significativa de DMO é apenas observada nos grupos etários a partir dos 50 anos, constituindo as classes etárias anteriores um grupo homogéneo do ponto de vista estatístico.

Colo do Fémur

Ao nível do colo do fémur, o pico de densidade óssea foi encontrado na classe etária 30-39 anos, verificando-se uma progressiva diminuição da DMO relacionada com a idade nas classes 40-49, 50-59 e a partir dos 60 anos, o que se verifica também na maior parte dos estudos[10,11,22,23], e sugere uma variabilidade pouco acentuada da DMO até aos 40 seguida de uma diminuição mais relevante a partir dos 50 anos, idade esta coincidente com o iní-

cio da menopausa para a maioria das mulheres.

Região Trocantérica

Na região trocantérica, o valor máximo de DMO encontrou-se na classe etária 30-39 anos. Nesta região observa-se uma marcada diminuição de DMO a partir da década dos 50 anos. Os valores obtidos para a nossa amostra, entre os 20-39 anos, encontram-se muito próximos de outro estudo[16] e ainda dos valores obtidos para a população norte americana no estudo *NHANES III*[23] embora o pico de densidade óssea, nesse estudo, tenha sido atingido na classe etária anterior.

Região Intertrocantérica

Na região intertrocantérica, o pico de densidade óssea foi encontrado no grupo etário dos 30-39 anos verificando-se uma certa homogeneidade na DMO entre os 20-49 anos. Tal como no trocanter, a partir dos 50 anos, o padrão de perda de massa óssea é bastante diferenciado de classe etária para classe etária o que reforça que a menopausa é um factor decisivo no estabelecimento do ritmo de perda de massa óssea[14,16].

Triângulo de Ward

Ao nível do triângulo de Ward, o valor máximo de DMO encontrou-se no escalão etário dos 20-29 anos verificando-se uma grande heterogeneidade no ritmo de decréscimo de DMO apresentando todas as classes etárias padrões significativamente diferentes de perda de massa óssea. Estes resultados podem ser parcialmente justificados pelo facto de o tipo de osso desta região apresentar uma elevada actividade metabólica, indiciando precocemente alterações de DMO[5,6].

A escolha dos locais anatómicos, coluna lombar L1-L4 e fémur proximal para avaliação de DMO, resulta do facto de serem as localizações que apresentam melhor correlação com o risco de fractura[4] e onde mais precocemente se verificam alterações a nível do osso trabecular e cortical. Há concordância nos valores de pico de densidade óssea encontrado no nosso estudo e os valores para pico de densidade óssea fornecido pelo fabricante, a nível do trocanter, região intertrocantérica, triângulo de Ward e fémur total[6]. Verificamos que as diferenças encontradas para pico de densidade óssea entre a base de referência Hologic® para mulheres jovens caucasianas da população norte-americana e o presente estudo resultam não só na avaliação do pico de densidade óssea, mas também da diferente amplitude dos desvios-padrão. Os desvios-padrão da base Hologic® são inferiores aos observados na nossa amostra, o que é consistente com o tamanho amostral utilizado para o cálculo destes valores, substancialmente superior ao da presente amostra. Tal facto implica um impacto significativo no cálculo dos *T – scores*, que, se calculados a partir da presente amostra, originam um défice relativo de massa óssea.

As principais fontes de bases de dados são ainda as fornecidas pelos fabricantes de equipamentos. Contudo, a fonte desses dados pode não ser a mais adaptada à população em estudo podendo induzir em erros sistemáticos consideráveis, ao nível do diagnóstico e avaliação do risco de fractura[25,26].

Actualmente, a comparabilidade inter-estudos pode, por vezes, ser comprometida, uma vez que também não existe acordo a nível metodológico na compilação e descrição dos dados. Para além disso, nos diversos estudos por nós analisados[10,11,13,16,22,23,27,28], verificamos também não existir homogeneidade a nível dos critérios de inclusão/exclusão das participantes. Embora *a priori* se encontrem descritos alguns factores de risco, com base nos quais poderíamos ter restringido a população estudada, optamos neste estudo por representar o mais fielmente possível a população em geral, incluindo mulheres com um grau de risco variável em relação à osteoporose.

Apesar das limitações atrás enumeradas, optámos por comparar a base de referência obtida a partir da nossa amostra para a coluna lombar e colo do fémur, com bases de referência utilizadas em outros estudos[29] para populações de diferentes países e regiões, Inglaterra, França, Espanha e Finlândia, população europeia e população americana.

Quando comparamos as bases de referência europeia e americana com a construída a partir da amostra (Figura 2), para a coluna lombar, observamos valores de DMO mais baixos na população portuguesa. Pode, no entanto, observar-se um decréscimo de DMO nas mulheres pré-menopáusicas na amostra estudada, e um paralelismo entre os 40 e 60 anos. Nos grupos etários mais velhos a diminuição constante da DMO na população americana contrasta com o valor relativamente constante na população europeia, e um ligeiro aumento na amostra estudada, provavelmente devido à já referida presença de alterações degenerativas a nível desta localização. Tal facto não é de estranhar, dado que no estudo EVOS, a frequência de

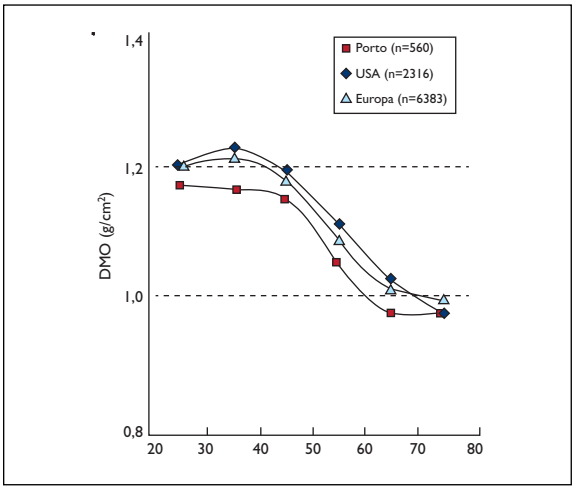

Figura 2. Distribuição dos valores de Densidade Mineral Óssea na amostra, população europeia e americana a nível da Coluna Lombar

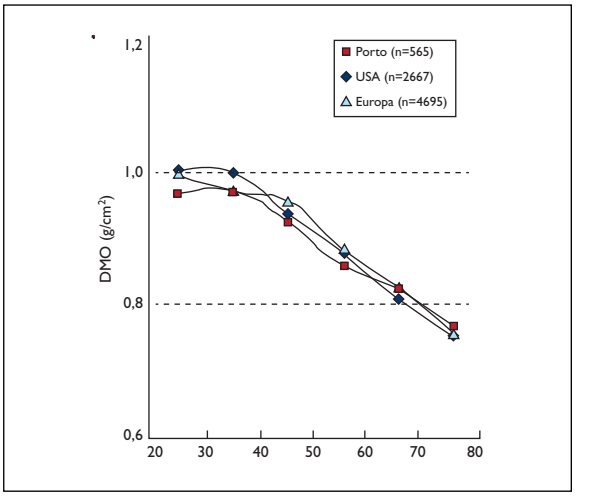

Figura 4. Distribuição dos valores de Densidade Mineral Óssea na amostra, população europeia e americana a nível do Colo do Fémur

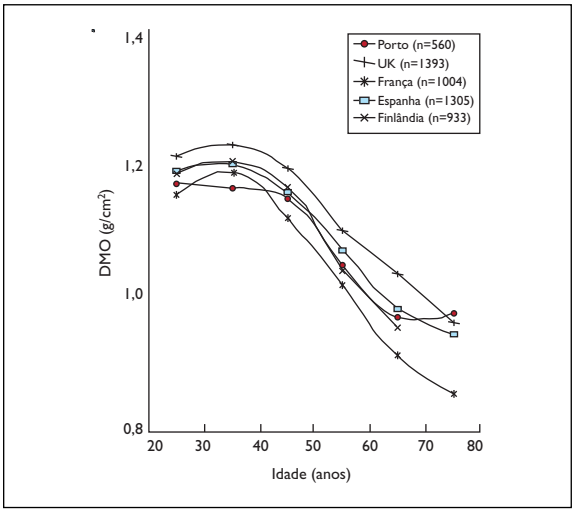

Figura 3. Distribuição dos valores de Densidade Mineral Óssea na amostra, população inglesa, francesa, espanhola e finlandesa a nível da Coluna Lombar

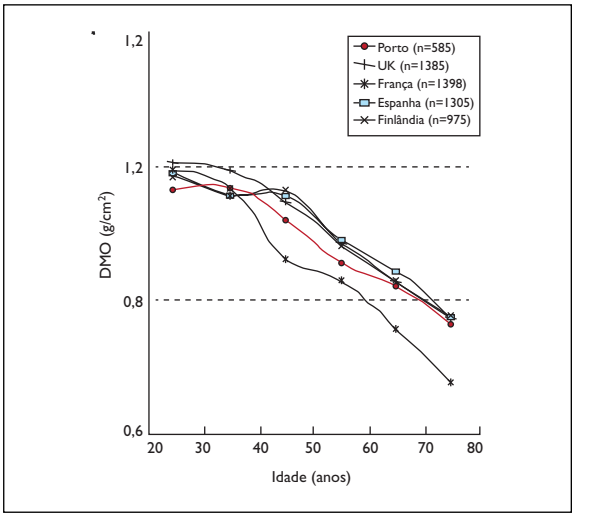

Figura 5. Distribuição dos valores de Densidade Mineral Óssea na amostra, população inglesa, francesa, espanhola e finlandesa a nível do Colo do Fémur

deformidades vertebrais na população feminina portuguesa é muito elevada.

A partir da análise comparativa entre os valores da base de referência relativa à coluna lombar usada neste estudo e a referente às populações inglesa, francesa, espanhola, finlandesa (Figura 3), observamos que o valor máximo de massa óssea se atinge mais cedo na nossa população, sendo também muito menos pronunciado e com valores de DMO inferiores aos das restantes populações. No entanto, à medida que a idade avança e devido a taxas de perda de massa óssea superiores na população francesa e finlandesa, estas apresentam valores de DMO inferiores aos obtidos na amostra portuguesa.

A nível do colo do fémur, o pico de densidade óssea da população portuguesa é mais baixo do que o encontrado para as populações europeia e americana (Figura 4). É curioso verificar que, para a faixa etária em que atingimos o pico de densidade óssea, a população europeia apresenta um valor semelhante ao valor da população portuguesa. A partir desta faixa etária os valores de DMO são semelhantes nas três populações.

Quando comparámos a DMO da amostra para esta localização com os valores de DMO das bases de referência de diferentes países (Figura 5), verificámos que o padrão de decréscimo na amostra estudada é semelhante ao padrão observado nas populações inglesa e francesa, embora os ingleses apresentem valores de DMO superiores e os franceses inferiores, com excepção das idades mais jovens (até cerca dos 40 anos). As restantes bases de referência apresentam padrões de evolução e valores de DMO praticamente idênticos.

De uma forma geral, constatamos que as diferenças observadas se mantêm aproximadamente constantes em qualquer uma das localizações, sendo ligeiramente mais acentuadas a nível da coluna do que a nível do colo do fémur.

Neste estudo foram construídas curvas de referência de densidade mineral óssea que descrevem a qualidade óssea ao longo da vida adulta numa população urbana de mulheres portuguesas.

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EVALUATION OF PATIENT CHARACTERISTICS AS PREDICTORS OF HEALTH STATUS IN KNEE OSTEOARTHRITIS PATIENTS REFERRED FOR PHYSICAL THERAPY

Rui Soles Gonçalves*, Jan Cabri**, João Páscoa Pinheiro***

Abstract

Objectives: The purpose of this cross sectional study was to estimate the contributions of patient characteristics to variation in joint-specific and generic health status in knee osteoarthritis (OA) patients referred for physical therapy.

Patients and Methods: The Portuguese Knee injury and Osteoarthritis Outcome Score (KOOS) and Medical Outcomes Study - 36 item Short Form (SF-36) questionnaires, and a form for the patient characteristics (gender, age, body mass index, profession, professional situation, educational level, marital status, duration of knee OA, involved knee and walking aids) were self-administered to 377 subjects with symptomatic knee OA (282 females, 95 males; age: 67.8 ± 8.2 years).

Results: Multiple stepwise regression analyses revealed that patient characteristics explained only 9.4% to 19.7% of the variance in KOOS subscales scores, and only 1.0% to 17.2% of the variance in SF-36 subscales scores.

Conclusion: Therefore, it can be concluded that the patient characteristics studied were limited predictors of joint-specific and generic health status in knee OA patients referred for physical therapy.

Keywords: Knee; Osteoarthritis; Patient Characteristics; Health Status.

Introduction

Knee osteoarthritis (OA) is a chronic problem that is usually accompanied by pain and functional limitation. This clinical condition has an adverse impact on various dimensions of health status and creates an increased demand for health care[1]. Self-reported health status measures focus on the perceived impact of a specific clinical condition on individuals and are therefore extensively used to assess the outcomes of health care interventions[2,3]. Joint-specific (e.g., Knee injury and Osteoarthritis Outcome Score - KOOS[4,5]) and generic health status questionnaires (e.g., Medical Outcomes Study - 36 item Short Form - SF-36 [6-8]) are commonly used in knee OA patients.

Physical therapy plays an important role in the management of knee OA[9]. Furthermore, there is increasing evidence that physical therapy reduces pain and improves physical function outcomes in knee OA patients[10] as measured by those self-reported health status questionnaires. However, these measures are still not widely used in clinical practice[11]. If physical therapists were able to get a broader perspective on the impact of knee OA on patients based on routinely collected information, it might be helpful in prioritizing access to physical therapy services and in designing specific and effective therapeutic interventions for individual patients. Patient characteristics data, which is usually available from physical therapy patient pre-admission records, would be particularly suitable for this purpose.

The objective of this paper was to estimate the contributions of patient characteristics to variation in joint-specific and generic health status in knee OA patients referred for physical therapy.

Patients and Methods

Subjects

The sample consisted of consecutive patients with symptomatic knee OA referred for physical thera-

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py at 12 Portuguese outpatient health care institutions during a 12-month period. Subjects were selected after obtaining informed consent and checking the inclusion and exclusion criteria. To be included in this cross sectional study, subjects had to have a diagnosis of uni- or bilateral knee OA according to the clinical and radiographic criteria of the American College of Rheumatology[12], to experience knee pain with a visual analogue scale (VAS) score of at least 30 mm in a 0-100 mm scale and to be aged 50 years or older. Subjects were excluded if they had received physical therapy treatments (for the knee) within the previous 30 days, had other lower limb osteoarthropathy, neurological disease, or any other disabling condition (e.g., back problems or widespread pain) or if they were unable to read or write Portuguese fluently. All outpatient health care institutions obtained approval from their respective review boards.

Measurements

Measurements were carried out in the physical therapy departments of the above mentioned outpatient health care institutions. All subjects were assessed during the first physical therapy session. Data were collected in a questionnaire format using the Portuguese versions of the self-reported measures mentioned below.

The KOOS[4,5], a joint-specific measure of health status, contains 42 items which cover five subscales: pain, other symptoms, function in daily living, function in sport and recreation, and knee-related quality of life. A score, from 0 (extreme problems) to 100 (no problems), is separately produced for each subscale according to the instructions of the KOOS user's guide[13]. The KOOS was cross-culturally adapted and validated to the Portuguese language[14].

The SF-36[6-8], a generic measure of health status, contains 36 items that covers eight subscales: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. A score, from 0 (worst possible health status) to 100 (best possible health status), is independently produced for each subscale according to the instructions of the SF-36 manual and interpretation guide[15]. The SF-36 was cross-culturally adapted and validated to the Portuguese language[16,17].

A form was used to acquire subject information on gender, age (years), body mass index ($kg.m^{-2}$), profession, professional situation, educational level, marital status, duration of knee OA (years), involved knee (knee with OA) and walking aids.

Statistical analyses

Continuous variables were described using mean and standard deviation values whereas categorical variables were described using frequency and percentage values.

Multiple regression analyses were used to estimate the contributions of different independent variables to variation in a dependent variable. The five KOOS subscales and the eight SF-36 subscales were used as dependent variables. Separate models were run for each dependent variable. The gender, age, body mass index, profession, professional situation, educational level, marital status, duration of knee OA, involved knee (knee with OA) and walking aids were used as independent variables. Independent categorical variables were dummy coded as dichotomous variables: Gender: 1 = female, 0 = male; Profession: 1 = manual, 0 = non-manual; Professional situation: 1 = economically active, 0 = not economically active; Educational level: 1 = complete basic/secondary/superior education level, 0 = only can read and write; Marital status: 1 = married, 0 = not/no longer married; Involved knee: 1 = bilateral, 0 = unilateral; Walking aids: 1 = aids necessary, 0 = no aids necessary. Profession was categorized using the Portuguese National Classification of Professions[18]: categories I, II, III, IV and V = non-manual; categories VI, VII, VIII and IX = manual.

The multiple regression analyses were carried out in two phases. In the first phase, Pearson's correlations and independent samples t-tests were used, as appropriate, to perform univariate analyses between all independent variables and each dependent variable. A P value of 0.20[19] was accepted as the level of significance to assure that potentially relevant independent variables were not excluded at this phase. In the second phase, all independent variables that were significantly univariately associated with each dependent variable were entered into multiple stepwise regression models (with stepping method criteria of probability of F to enter ≤ 0.05 and F to remove ≥ 0.10). All models met the assumptions of multiple regression in terms of linearity, homoscedasticity, normality, independence and non-multicollinearity.

All statistical analyses were conducted using Statistical Package for the Social Sciences, SPSS® 15.0 for Windows® (SPSS Inc., Chicago, IL, USA).

Results

A total of 377 patients participated in this study. The descriptive statistics are presented in Tables I and II. A total score could be obtained for all KOOS and SF-36 subscales for all patients.

Tables III and IV display the associations between health status and patient characteristics and highlight the potentially relevant patient characteristics that were statistically significantly associated with each of the KOOS and SF-36 subscales and, consequently, were entered into multiple stepwise regression models.

Table V shows the multiple stepwise regression models of knee-specific health status. In the final models, the values of adjusted R^2 indicated that patient characteristics explained only 9.4% to 19.7% of the variance in KOOS subscales scores. Longer duration of knee OA (negative), need for walking aids (negative) and complete basic/secondary/superior education level (positive) accounted for 9.4% of the variance in the KOOS pain subscale score, while longer duration of knee OA (negative) and need for walking aids (negative) accounted for 10.0% of the variance in the KOOS other symptoms subscale score. Need for walking aids (negative), longer duration of knee OA (negative), higher body mass index (negative), complete basic/secondary/superior education level (positive) and older age (negative) accounted for 19.7% of the variance in the KOOS function in daily living subscale score, while need for walking aids (negative), longer duration of knee OA (negative), complete basic/secondary/superior education level (positive) and higher body mass index (negative) accounted for 16.2% of the variance in the KOOS function in sport and recreation subscale score. Need for walking aids (negative), higher body mass index (negative), longer duration of knee OA (negative) and manual profession (negative) were significant predictors of the KOOS knee-related quality of life subscale score; the four variable accounted for 15.3% of the variance.

Table VI shows the multiple stepwise regression models of generic health status. In the final models, the values of adjusted R^2 indicated that patient characteristics explained only 1.0% to 17.2% of the variance in SF-36 subscales scores. Need for walking aids (negative), manual profession (negative), being economically active (positive) and being female (negative) accounted for 17.2% of the variance in the SF-36 physical functioning subscale score, while complete basic/secondary/superior education level (positive), need for walking aids (negative) and higher body mass index (negative) accounted

Table I. Patients' characteristics (N = 377)

Characteristics	Data
Gender	
Female	282 (74.8)
Age (years)	67.8 ± 8.2
Body mass index (kg.m-2)	29.2 ± 4.4
Profession	
Manual	299 (79.3)
Professional situation	
Not economically active	310 (82.2)
Educational level	
Only can read and write	308 (81.7)
Marital status	
Married	271 (71.9)
Duration of knee OA (years)	10.6 ± 8.6
Involved knee (knee with OA)	
Bilateral	209 (55.4)
Walking aids	
No aids necessary	272 (72.1)

Continuous variables: mean ± standard deviation; Categorical variables: frequency (percentage).

Table II. Knee-specific and generic health status (N = 377)

Questionnaires subscales scores	Mean ± SD
KOOS (points)	
Pain (PA)	36.7 ± 15.2
Other symptoms (OS)	40.2 ± 17.9
Function in daily living (DL)	37.4 ± 16.4
Function in sport and recreation (SR)	15.2 ± 18.5
Knee-related quality of life (QL)	28.6 ± 18.1
SF-36 (points)	
Physical functioning (PF)	31.7 ± 20.5
Role-physical (RP)	39.1 ± 23.6
Bodily pain (BP)	26.6 ± 16.7
General health (GH)	43.2 ± 17.8
Vitality (VT)	34.8 ± 18.9
Social functioning (SF)	60.2 ± 26.4
Role-emotional (RE)	56.2 ± 28.9
Mental health (MH)	55.2 ± 23.5

KOOS and SF- 36 are 0-100 points, worst to best.

Table III. Significance of differences in health status between groups based on patients' characteristics (N = 377)

Patients' characteristics	N	Health status: KOOS subscales PA	OS	DL	SR	QL	SF-36 subscales PF	RP	BP	GH	VT	SF	RE	MH
Gender (P)		0.420	0.821	0.213	0.999	0.820	***0.025***	0.265	***0.027***	***0.005***	**0.106**	**0.128**	**0.180**	**0.000**
Female (Mean±SD)	282	36.3±15.4	40.1±17.6	36.8±16.4	15.2±18.7	28.5±17.9	30.3±19.7	38.3±23.1	25.5±16.7	41.7±17.2	33.8±18.9	59.0±26.5	55.0±28.3	52.8±23.3
Male (Mean±SD)	95	37.8±14.8	40.6±18.9	39.3±16.3	15.2±18.1	29.0±18.7	35.7±22.1	41.4±24.7	29.8±16.4	47.5±19.0	37.5±18.9	63.8±25.9	59.6±30.8	62.5±22.7
Profession (P)		***0.009***	**0.067**	***0.002***	***0.010***	***0.002***	**0.000**	***0.004***	***0.002***	**0.095**	**0.181**	***0.030***	**0.001**	***0.010***
Manual (Mean±SD)	299	35.6±15.2	39.4±17.6	36.1±15.5	14.0±18.5	27.0±17.1	29.2±19.3	37.0±22.0	25.2±16.0	42.4±17.5	34.1±18.7	58.7±26.7	53.6±27.8	53.6±23.2
Non-manual (Mean±SD)	78	40.7±14.8	43.5±18.5	42.5±18.6	20.0±17.9	34.9±20.4	41.1±22.1	47.0±27.5	31.7±18.3	46.2±18.8	37.3±19.6	66.0±24.5	66.0±31.2	61.3±23.9
Professional situation (P)		0.219	0.560	**0.000**	***0.006***	**0.001**	**0.000**	***0.004***	***0.044***	***0.005***	0.813	**0.000**	**0.000**	**0.000**
Economically active (Mean±SD)	67	38.8±16.2	41.2±13.9	43.9±17.5	20.8±19.9	35.3±19.2	41.8±19.5	46.5±26.0	30.3±17.0	48.7±16.6	34.2±19.9	71.6±25.3	68.3±31.4	64.4±24.2
Not economically active (Mean±SD)	310	36.2±15.0	40.0±18.6	36.4±15.9	14.0±18.0	27.2±17.5	29.5±20.0	37.5±22.7	25.8±16.6	41.9±17.9	34.9±18.8	57.8±26.0	53.5±27.8	53.3±22.9
Educational level (P)		**0.001**	***0.034***	**0.000**	**0.000**	***0.003***	**0.001**	**0.001**	***0.002***	**0.110**	0.786	0.326	***0.019***	0.569
Complete basic/ /secondary/superior education level (Mean±SD)	69	42.3±14.3	44.4±17.2	43.8±18.1	23.2±20.3	35.3±20.6	40.2±24.4	49.2±27.9	32.1±18.5	46.3±19.9	35.3±19.6	62.9±23.8	64.4±32.8	56.7±24.8
Only can read and write (Mean±SD)	308	35.4±15.2	39.3±17.9	36.0±15.7	13.4±17.6	27.1±17.1	29.8±19.0	36.9±21.9	25.3±16.0	42.5±17.3	34.6±18.8	59.7±27.0	54.3±27.7	54.9±23.2
Marital status (P)		0.297	0.416	0.609	0.568	0.689	0.633	0.572	0.294	0.229	0.501	0.660	0.851	0.926
Married (Mean±SD)	271	36.2±14.9	39.8±17.4	37.7±16.1	15.5±18.9	28.4±17.9	31.4±20.7	38.7±23.2	26.0±16.4	43.8±17.9	34.4±19.5	59.9±26.8	56.0±29.2	55.3±23.6
Not/no longer married (Mean±SD)	106	38.0±16.0	41.4±19.0	36.7±17.3	14.3±17.5	29.2±18.6	32.5±19.9	40.2±24.6	28.0±17.6	41.4±17.8	35.8±17.4	61.2±25.6	56.6±28.5	55.0±23.2
Involved knee / knee with OA (P)		0.495	0.710	**0.142**	0.505	**0.116**	***0.008***	0.708	0.434	**0.000**	0.629	0.275	0.373	0.684
Bilateral (Mean±SD)	209	36.2±14.8	39.9±18.7	36.3±16.1	14.6±19.3	27.3±18.3	30.1±19.6	38.7±23.7	27.2±17.2	40.1±17.3	35.2±18.9	58.9±25.2	55.0±28.5	54.8±22.8
Unilateral (Mean±SD)	168	37.3±15.8	40.6±16.8	38.8±16.8	15.9±17.6	30.3±17.7	33.7±21.4	39.6±23.4	25.8±16.1	46.9±17.8	34.2±19.0	61.9±27.9	57.6±29.5	55.8±24.3
Walking aids (P)		**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.001**	**0.000**	**0.055**	***0.027***	**0.000**	**0.000**	***0.002***
Aids necessary (Mean±SD)	105	31.4±15.0	33.7±17.5	28.1±13.0	6.6±12.9	20.8±15.6	20.8±17.2	32.5±20.9	20.4±15.7	40.0±20.3	31.2±19.2	50.1±27.1	46.2±27.4	49.3±24.1
No aids necessary (Mean±SD)	272	38.7±14.9	42.8±17.4	41.0±16.2	18.5±19.3	31.7±18.1	35.9±20.1	41.7±24.1	28.9±16.5	44.3±16.7	36.1±18.7	64.1±25.1	60.0±28.7	57.5±22.9

Independent samples t test (two-tailed P values). PA = Pain; OS = Other symptoms; DL = Function in daily living; SR = Function in sport and recreation; QL = Knee-related quality of life; PF = Physical functioning; RP = Role-physical; BP = Bodily pain; GH = General health; VT = Vitality; SF = Social functioning; RE = Role-emotional; MH = Mental health. KOOS and SF-36 are 0-100 points, worst to best. Gender: female vs. male; Profession: manual vs. non-manual; Professional situation: economically active vs. not economically active; Educational level: complete basic/secondary/superior education level vs. only can read and write; Marital status: married vs. not/no longer married; Involved knee: bilateral vs. unilateral; Walking aids: aids necessary vs. no aids necessary. Significant differences: P ≤0.001 in bold/underline; P ≤0.05 in bold/italic; P ≥0.20 in bold. When significant differences were found, the groups female, manual, bilateral and aids necessary consistently obtained the lowest scores, and the groups economically active and complete basic/secondary/superior education level consistently obtained the highest scores.

Table IV. Correlation coefficients between health status and patients' characteristics (N = 377)

Patients' characteristics	Health status												
	KOOS subscales					SF-36 subscales							
	PA	OS	DL	SR	QL	PF	RP	BP	GH	VT	SF	RE	MH
Age (years)	***-0.12***	-0.01	**-0.28**	**-0.23**	**-0.20**	**-0.20**	**-0.18**	**-0.07**	**-0.07**	0.01	***-0.13***	**-0.16**	-0.03
Body mass index ($kg.m^{-2}$)	***-0.13***	***-0.13***	**-0.18**	**-0.19**	**-0.22**	***-0.13***	***-0.16***	**-0.18**	***-0.16***	-0.01	***-0.13***	**-0.09**	-0.04
Duration of knee OA (years)	**-0.22**	**-0.26**	**-0.25**	**-0.26**	**-0.24**	***-0.15***	***-0.14***	**-0.19**	**-0.17**	**-0.10**	***-0.13***	**-0.09**	-0.01

Pearson's correlation coefficients.
PA = Pain; OS = Other symptoms; DL = Function in daily living; SR = Function in sport and recreation; QL = Knee-related quality of life; PF = Physical functioning; RP = Role-physical; BP = Bodily pain; GH = General health; VT = Vitality; SF = Social functioning; RE = Role-emotional; MH = Mental health.
KOOS and SF-36 are 0-100 points, worst to best.
Significant correlations: P ≤ 0.001 in bold/underline; P ≤ 0.05 in bold/italic; P ≤ 0.20 in bold.
Medium correlation (|r| = 0.30 to 0.49); small correlation (|r| < 0.30)[28].

Table V. Multiple stepwise regression models of knee-specific health status (N = 377)

KOOS subscales	Step	Predictors	Adjusted R^2	F	df	P*	Beta†	P‡
PA	1	Duration of knee OA (years)	*0.048*	*19.9*	*1,375*	*< 0.001*	**-0.174**	**0.001**
	2	Walking aids	*0.079*	*17.1*	*2,374*	*< 0.001*	**-0.179**	**<0.001**
	3	Educational level	**0.094**	**14.0**	**3,373**	**< 0.001**	**0.135**	**0.007**
OS	1	Duration of knee OA (years)	*0.067*	*28.1*	*1,375*	*< 0.001*	**-0.233**	**< 0.001**
	2	Walking aids	**0.100**	**21.9**	**2,374**	**< 0.001**	**-0.190**	**< 0.001**
DL	1	Walking aids	*0.122*	*53.4*	*1,375*	*< 0.001*	**-0.271**	**< 0.001**
	2	Duration of knee OA (years)	*0.158*	*36.2*	*2,374*	*< 0.001*	**-0.135**	**0.006**
	3	Body mass index ($kg.m^{-2}$)	*0.175*	*27.6*	*3,373*	*< 0.001*	**-0.135**	**0.004**
	4	Educational level	*0.187*	*22.7*	*4,372*	*< 0.001*	**0.110**	**0.021**
	5	Age (years)	**0.197**	**19.4**	**5,371**	**< 0.001**	**-0.121**	**0.021**
SR	1	Walking aids	*0.081*	*34.1*	*1,375*	*< 0.001*	**-0.243**	**< 0.001**
	2	Duration of knee OA (years)	*0.125*	*27.8*	*2,374*	*< 0.001*	**-0.182**	**< 0.001**
	3	Educational level	*0.147*	*22.6*	*3,373*	*< 0.001*	**0.144**	**0.003**
	4	Body mass index ($kg.m^{-2}$)	**0.162**	**19.2**	**4,372**	**< 0.001**	**-0.135**	**0.005**
QL	1	Walking aids	*0.070*	*29.2*	*1,375*	*< 0.001*	**-0.219**	**< 0.001**
	2	Body mass index ($kg.m^{-2}$)	*0.109*	*24.0*	*2,374*	*< 0.001*	**-0.178**	**< 0.001**
	3	Duration of knee OA (years)	*0.140*	*21.4*	*3,373*	*< 0.001*	**-0.174**	**< 0.001**
	4	Profession	**0.153**	**18.0**	**4,372**	**< 0.001**	**-0.126**	**0.009**

PA = Pain; OS = Other symptoms; DL = Function in daily living; SR = Function in sport and recreation; QL = Knee-related quality of life. KOOS subscales are 0-100 points, worst to best. Profession: 1 = manual, 0 = non-manual; Educational level: 1 = complete basic/secondary/superior education level, 0 = only can read and write; Walking aids: 1 = aids necessary, 0 = no aids necessary. *Statistical significance of the models (all steps). † Standardized coefficients of the predictors included in the final model. ‡ Statistical significance of the predictors include in the final model. Data from the final steps in bold. Data from the previous steps in italic.

for 7.6% of the variance in the SF-36 role--physical subscale score. Need for walking aids (negative), higher body mass index (negative), longer duration of knee OA (negative), manual profession (negative) and being female (negative) accounted for 11.2% of the variance in the SF-36 bodily pain subscale score. Bilateral knee OA (negative), longer duration of knee OA (negative), being female (negative) and higher body mass index (negative) accounted for 7.6% of the variance in the SF-36 general health subscale score. Only need for walking aids (negative) was a significant predictor of the SF-36 vitality subscale

Table VI. Multiple stepwise regression models of generic health status (N = 377)

SF-36 subscales	Step	Predictors	Adjusted R^2	F	df	P*	Beta†	P‡
PF	1	Walking aids	*0.106*	*45.8*	*1,375*	*< 0.001*	**-0.294**	**< 0.001**
	2	Profession	*0.146*	*33.0*	*2,374*	*< 0.001*	**-0.177**	**< 0.001**
	3	Professional situation	*0.164*	*25.6*	*3,373*	*< 0.001*	**0.133**	**0.007**
	4	Gender	**0.172**	**20.5**	**4,372**	**< 0.001**	**-0.100**	**0.036**
RP	1	Educational level	*0.039*	*16.1*	*1,375*	*< 0.001*	**0.177**	**< 0.001**
	2	Walking aids	*0.062*	*13.5*	*2,374*	*< 0.001*	**-0.157**	**0.002**
	3	Body mass index ($kg.m^{-2}$)	**0.076**	**11.3**	**3,373**	**< 0.001**	**-0.128**	**0.011**
BP	1	Walking aids	*0.049*	*20.6*	*1,375*	*< 0.001*	**-0.193**	**< 0.001**
	2	Body mass index ($kg.m^{-2}$)	*0.077*	*16.7*	*2,374*	*< 0.001*	**-0.146**	**0.003**
	3	Duration of knee OA (years)	*0.093*	*13.8*	*2,373*	*< 0.001*	**-0.125**	**0.012**
	4	Profession	*0.104*	*11.9*	*3,372*	*< 0.001*	**-0.112**	**0.023**
	5	Gender	**0.112**	**10.5**	**4,371**	**< 0.001**	**-0.103**	**0.035**
GH	1	Involved knee (knee with OA)	*0.033*	*13.9*	*1,375*	*< 0.001*	**-0.147**	**0.004**
	2	Duration of knee OA (years)	*0.055*	*12.0*	*2,374*	*< 0.001*	**-0.144**	**0.004**
	3	Gender	*0.069*	*10.3*	*3,373*	*< 0.001*	**-0.122**	**0.015**
	4	Body mass index ($kg.m^{-2}$)	**0.076**	**8.7**	**4,372**	**< 0.001**	**-0.101**	**0.049**
VT	1	Walking aids	**0.010**	**4.9**	**1,375**	**0.027**	**-0.114**	**0.027**
SF	1	Walking aids	*0.054*	*22.6*	*1,375*	*< 0.001*	**-0.208**	**< 0.001**
	2	Professional situation	*0.079*	*17.1*	*2,374*	*< 0.001*	**0.156**	**0.002**
	3	Body mass index ($kg.m^{-2}$)	**0.087**	**12.9**	**3,373**	**< 0.001**	**-0.102**	**0.041**
RE	1	Walking aids	*0.043*	*18.0*	*1,375*	*< 0.001*	**-0.178**	**< 0.001**
	2	Professional situation	*0.067*	*14.5*	*2,374*	*< 0.001*	**0.141**	**0.006**
	3	Profession	**0.081**	**12.0**	**3,373**	**< 0.001**	**-0.129**	**0.011**
MH	1	Professional situation	*0.030*	*12.7*	*1,375*	*< 0.001*	**0.134**	**0.009**
	2	Gender	*0.052*	*11.2*	*2,374*	*< 0.001*	**-0.165**	**0.001**
	3	Walking aids	**0.068**	**10.2**	**3,373**	**< 0.001**	**-0.140**	**0.006**

PF = Physical functioning; RP = Role-physical; BP = Bodily pain; GH = General health; VT = Vitality; SF = Social functioning; RE = Role-emotional; MH = Mental health. SF-36 subscales are 0-100 points, worst to best. Gender: 1 = female, 0 = male; Profession: 1 = manual, 0 = non-manual; Professional situation: 1 = economically active, 0 = not economically active; Educational level: 1 = complete basic/secondary/superior education level, 0 = only can read and write; Involved knee: 1 = bilateral, 0 = unilateral; Walking aids: 1 = aids necessary, 0 = no aids necessary. * Statistical significance of the models (all steps). † Standardized coefficients of the predictors included in the final model. ‡ Statistical significance of the predictors include in the final model. Data from the final steps in bold. Data from the previous steps in italic.

score and accounted for 1.0% of the variance. Need for walking aids (negative), manual profession (negative) and higher body mass index (negative) accounted for 8.7% of the variance in the SF-36 social functioning subscale score. Need for walking aids (negative), being economically active (positive) and manual profession (negative) accounted for 8.1% of the variance in the SF-36 role-emotional subscale score. Being economically active (positive), being female (negative) and need for walking aids (negative) accounted for 6.8% of the variance in the SF-36 mental health subscale score. Marital status was not a significant predictor of any of the KOOS or SF-36 subscales scores.

Discussion

In this study we assessed the contributions of patient characteristics to variation in joint-specific and generic health status, which were shown to be limited in the patients evaluated. Thus, in clinical practice, physical therapists should not use this routinely collected information to try to get a broader perspective on the impact of knee OA on their patients.

Of the ten patient characteristics studied, six (i.e. walking aids, duration of knee OA, body mass index, educational level, profession and age) were significant predictors of at least one dimension of the knee-

specific health status. Moreover, eight characteristics (i.e. walking aids, body mass index, gender, professional situation, profession, duration of knee OA, educational level and involved knee) were significant predictors of at least one dimension of the generic health status. The direction of the associations between health status and patient characteristics was plausible and consistent with prior research in OA[20-23]. Overall, the need for walking aids was the best significant predictor of worse health status. In fact, the aforementioned characteristic only was not a significant predictor of the SF-36 general health dimension. This is not surprising considering that the need for walking aids seems to be determined by disability, pain and age-related impairments[24]. Marital status was the only variable that was not a significant predictor of any dimension of health status. The quality of support received from the spouse might be a better determinant[25].

Need for walking aids, longer duration of knee OA and higher body mass index represented better significant predictors for worse knee-specific health status and completed basic/secondary/superior education level was the best significant predictor of better knee-specific health status. Need for walking aids, higher body mass index and being female were the best significant predictors of worse generic health status and being economically active was the best significant predictor for a better generic health status. Other studies found similar results[20-23]. Helplessness, education level and body mass index were identified as determinants of pain severity in knee OA patients by Creamer et al[20]. Golightly & Dominick[21] found an association between longer duration of OA, presence of hip OA and lower income, and worse osteoarthritis-specific health status in Caucasian veterans. In a study of Salaffi et al[22], age, lower educational level, being female and chronic co-morbidity proved to be associated with physical function in patients with symptomatic peripheral OA. Paradowski et al[23] suggested that, in patients with early knee OA, the natural history of pain and function may be related to patient characteristics such as age and body mass index.

Although nearly all studied patient characteristics were significant predictors in at least one of the multiple stepwise regression models of health status, they cumulatively explained not more than 19.7% of the variance in knee-related health status and no more than 17.2% of the variance in generic health status. Final models explained more variance for the physical function subscales than for the other subscales, either for the KOOS (function in daily living) or for the SF-36 (physical functioning). This finding suggests that, even for physical function dimensions, a substantial amount of the variance in health status may actually be explained by other predictors that were not collected in this study. Nevertheless, it is also possible that the low amount of variance explained by the final models was influenced by the use of seven categorical independent variables dummy coded as dichotomous variables, which imply a low observed variability.

Some limitations of this study should be also mentioned. First, the sample used may not be representative for the entire population of Portuguese patients with knee OA referred for physical therapy. In fact, this study used a convenience sampling method. Second, the study sample is relatively homogeneous with respect to the studied patient characteristics. This might be one of the reasons that contributed to the low proportion of explained variation in health status. Third, only a small number of patient characteristics were evaluated. There are other patient characteristics (e.g., consumption of medication) that might help to explain a greater amount of variation in knee-specific and generic health status. Fourth, owing to practical reasons, radiographic severity of knee OA was not recorded. Although no consensus appears to exist about the association between radiographic severity of knee OA and self-reported knee pain and functional limitation[26,27], this could have been a confounding factor with regard to the relationship between patient characteristics and health status dimensions. Finally, neither correlation nor prediction necessarily indicate causation. Moreover, the cross-sectional nature of this study precludes any conclusions regarding causation, and also the possibility of reverse causation cannot be excluded.

Conclusion

In conclusion, the patient characteristics studied were limited predictors of joint-specific and generic health status in knee OA patients referred for physical therapy.

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PHYSIOTHERAPY IN RHEUMATOID ARTHRITIS: DEVELOPMENT OF A PRACTICE GUIDELINE

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Abstract

Background: To improve the quality of the physiotherapy management in patients with rheumatoid arthritis (RA) a Dutch practice guideline, based on current scientific evidence and best practice, was developed. This guideline comprised all elements of a structured approach (assessment, treatment and evaluation) and was based on the International Classification of Functioning, disability and Health (ICF) and the ICF core sets for RA.

Methods: A guideline steering committee, comprising 10 expert physiotherapists, selected topics concerning the guideline chapters initial assessment, treatment and evaluation. With respect to treatment a systematic literature search was performed using various databases, and the evidence was graded (1-4). For the initial assessment and evaluation mainly review papers and textbooks were used. Based on evidence and expert opinion, recommendations were formulated. A first draft of the guideline was reviewed by 10 experts from different professional backgrounds resulting in the final guideline.

Results: In total 7 topics were selected. For the initial assessment, three recommendations were made. Based on the ICF core sets for RA a list of health problems relevant for the physiotherapist was made and completed with red flags and points of attention. Concerning treatment, three recommendations were formulated; both exercise therapy and education on physiotherapy were recommended, whereas passive interventions (delivery of heat or cold, mechanical, electric and electromagnetic energy, massage, passive mobilization/manipulation and balneotherapy) were neither recommended nor discouraged. For treatment evaluation at the level of activities and participation, the Health Assessment Questionnaire was recommended. For evaluating specific body structures and functions the handheld dynamometer, 6-minute walk test or Ästrand bicycle test (including Borg-scale for rating the perceived exertion), Escola Paulista de Medicina Range of Motion Scale and a Visual Analog Scale for pain and morning stiffness were recommended.

Conclusion: This physiotherapy practice guideline for RA included seven recommendations on the initial assessment, treatment and evaluation, which were all based on the ICF and the ICF Core Set for RA. The implementation of the guideline in clinical practice needs further evaluation.

Keywords: Rheumatoid arthritis; Physiotherapy; Guideline; Clinical practice

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Introduction

Rheumatoid arthritis (RA) is a disease with a considerable impact in many patients, often requiring, apart from medical treatment, the involvement of

various health care providers[1]. Physiotherapy is a relatively frequently applied treatment, with about 25-40% of patients with RA being treated by a physiotherapist over a period of one year[1,2]. Physiotherapy is recommended in a number of multidisciplinary international[3-7]. In addition to multidisciplinary guidelines, there are two Canadian guidelines on RA management specifically for the physical therapist[8,9]. Although these latter guidelines include detailed information with regard to various physiotherapy interventions, no information with regard to the physiotherapy diagnostic and evaluation processes is provided.

Since no physiotherapy specific guideline including all aspects of the physiotherapy management of RA patients is currently available, the aim of the present study was to develop a set of recommendations including the initial diagnostic process, physiotherapy interventions and their evaluation.

Methods

The development of the guideline took place between May 2006 and October 2008. The guideline was developed according to current international methods for guideline development and implementation[18]. The guideline was developed by a Guideline Steering Committee comprising 10 expert physical therapists. Two members of the committee (EH and TVV) proposed a preliminary list of topics to the Guideline Steering Committee based on textbooks, umbrella reviews and systematic reviews, and currently available physiotherapy guidelines. During a consensus meeting, a final list of 7 topics (3 for initial assessment, 3 for treatment, and 1 for evaluation) was selected (Table I).

The various steps for the actual guideline development comprised: literature search (step 1); grading of evidence (step 2); formulation of recommendations (step 3); and external review (step 4).

Step 1: Literature search

With respect to the initial physiotherapy assessment, the preliminary search of the literature yielded little literature specifically addressing and substantiating individual topics within this dimension. Therefore, to summarize the evidence, we primarily used textbooks, review articles, umbrella review articles, and current guidelines on other, related conditions.

For the therapeutic process an intervention-specific literature search was performed up to June 2007 in the MEDLINE, EMBASE, CINAHL, Pedro, Web of Science and Cochrane databases to identify reviews, meta-analysis, and randomized controlled trials (RCTs). The central search strategy 'Arthritis, Rheumatoid' (MESH) was combined with other MESH-headings and/or free text words such as 'physiotherapy', 'physical therapy' (MESH), 'physical therapy modalities' (MESH), 'exercise therapy', 'physical education and training' (MESH).

Table I. From scientific evidence and expert opinion to recommendations according to the EBRO (Evidence Based Recommendation Development), which is in line with international classification scheme[13], such as the NICE approach

Grade of evidence	A1	Meta-analyses (systematic reviews), which include at least two RCTs at quality level
	A2	that show consistent results between studies
	A2	RCTs of a good methodological quality (randomized double blind controlled studies) with sufficient power and consistency
	B	RCTs of a moderate methodological quality of with insufficient power, or non-randomized, cohort of patient-control group study involving intergroup comparisons
	C	Patient series
	D	Expert opinion
Level of recommendation	1	One A1 study or at least two A2 studies
	2	One A2 study or at least two B studies
	3	One B or multiple C studies
	4	Expert opinion

RCT: Randomized Controlled Trial

Studies were selected if sufficient data were reported with regard to the physiotherapy treatment of RA patients. In case no RCTs were found controlled clinical trials (CCTs) or other type of studies such as observational studies were identified and selected. A detailed description of this literature search, confined to the intervention dynamic exercise therapy, was published separately[21].

With respect to evaluation, a search strategy up to June 2007 was applied within the same databases as those used for treatment. The central search strategy was combined with 'sensitivity and specificity' (MESH), 'expertise test', 'physical examination' (MESH), and 'treatment outcome' (MESH).

Step 2: Categorizing evidence

The selected literature was critically appraised by assessing the type and quality of the study design. Evidence was graded according to the EBRO (a Dutch acronym for Evidence Based Recommendation Development) criteria (Table I), which is in line with international classification schemes[22], such as the NICE (National Institute of Clinical Effectiveness) approach. EBRO is an initiative of the Dutch Cochrane Centre and the Dutch Institute for Healthcare Improvement (CBO), a member of the Guidelines International Network (GIN)[23].

Step 3: Strength of recommendations

By means of six consensus meetings of the Guideline Steering Committee recommendations were formulated and their strength graded A–D, based on the category of efficacy evidence (Table I).

Step 4: External Review by Guideline Review Committee

A first draft of the guideline was sent to the members of the Guideline Review Committee. The Guideline Review Committee included a rheumatologist, a clinical nurse specialist, an orthopaedic surgeon, a rehabilitation specialist, a social worker, an occupational therapist and a psychologist. Furthermore, representatives of the Dutch Arthritis Foundation and the Arthritis Patient Organization participated in the Guideline Review Committee. Comments were collected by e-mail, discussed with the Guideline Steering Committee and incorporated in the final draft. After adaptation, the final draft of the guideline was reviewed and pilot tested by 50 physiotherapists. Based on their comments minor comments concerning the feasibility of the measurement instruments, including lack of time and space to perform are taken into account and the final guideline was finished.

Results

Initial assessment process

In the Netherlands, physiotherapy can be accessed with or without a referral from a physician (also called "direct access"). The Guideline Steering Committee considered the following information essential for the physiotherapist: verification of the diagnosis, extent of radiological joint damage, the presence of co-morbidity and current and expected disease activity under the present medical management. This information should be included in the referral. In case of insufficient information or direct access the physiotherapist should contact the patient's rheumatologist.

The initial assessment comprises history taking, physical examination and analysis. History taking and physical examination are performed to get a comprehensive overview of the patient's health status. This overview includes screening for red flags and points of attention. With the analysis, the patient's main limitations and impairments are prioritized, and treatment goals and a treatment plan are formulated. The total initial assessment process is described in Figure 1.

Clinical question 1: In which way the patient's health status can be assessed?

RECOMMENDATION 1:

The physiotherapist should assess the patient's health status primarily in terms of activity limitations and participation restrictions. In addition, the therapist may also assess impairments of body functions and structures, as well as personal and environmental factors, insofar as these relate to the limitations and restrictions (level 4).

For the initial assessment, the physiotherapist should use an overview of the most relevant health problems in RA patients, based on the ICF Core Set for Rheumatoid Arthritis (short version)[13-17], completed with a number of personal factors (Figure 2) This overview facilitates the structuring, organizational and documentation of the rehabilitation process. It enables physiotherapists to coordinate their actions. The key elements of this process are: the initial assessment, treatment and evaluation[12].

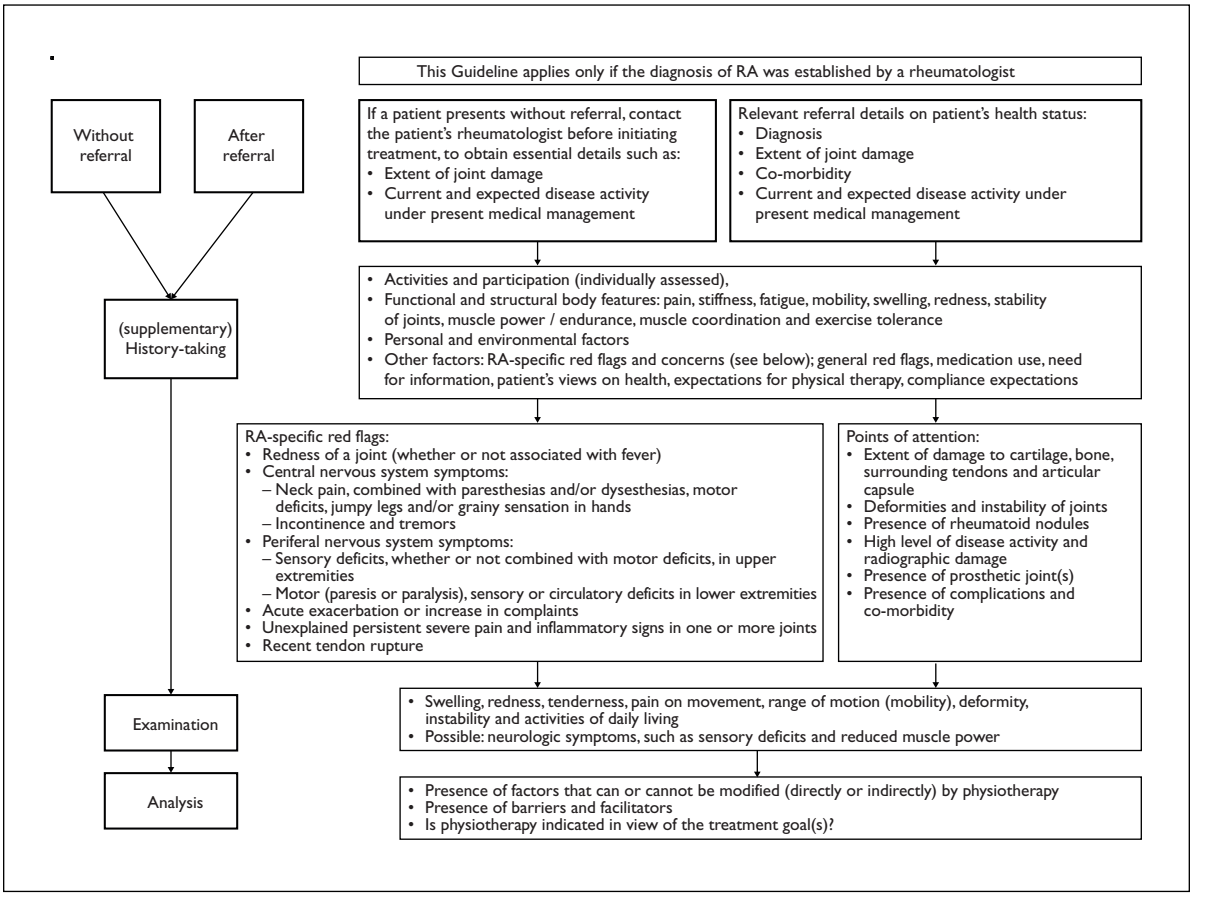

Figure 1. Overview inital assessment

Clinical question 2: Which contraindications for physical therapy should be taken into account in patients with RA?

RECOMMENDATION 2:
Physiotherapists should evaluate the presence of "red flags" and points of attention (level 4).
The following specific red flags in RA patients were defined: redness of a joint (whether or not accompanied by fever); symptoms relating to the central nervous system (neck pain, in combination with paraesthesias and/or dysaesthesias, motor deficits, jumpy legs, and/or a grainy sensation in the hands, incontinence and tremors); peripheral neurological symptoms (sensory deficits, whether or not in combination with motor deficits, in the upper extremities, motor deficits (paresis or paralysis), sensory or circulatory deficits in the lower extremities); acute exacerbation or increased complaints; unexplained persistent severe pain and inflammatory signs in one or more joints; recent tendon rupture (e.g. of the extensor digitorum, extensor pollicis, or biceps brachii muscle).

The following specific points of attention in RA patients were defined: extent of damage to cartilage, bone, surrounding tendons and articular capsule; deformities and instability of joints; presence of rheumatoid nodules; high level of disease activity and radiographic damage; presence of joint prostheses; and presence of complications of RA or co-morbidity.

Clinical Question 3: How does the physical therapist set treatment goals?

RECOMMENDATION 3:
Based on the information obtained in the initial assessment, the physiotherapist should define the therapeutic goals (level 4).
Based on of the description of the health status and environmental and personal factors, individual treatment goals should be defined. Goal

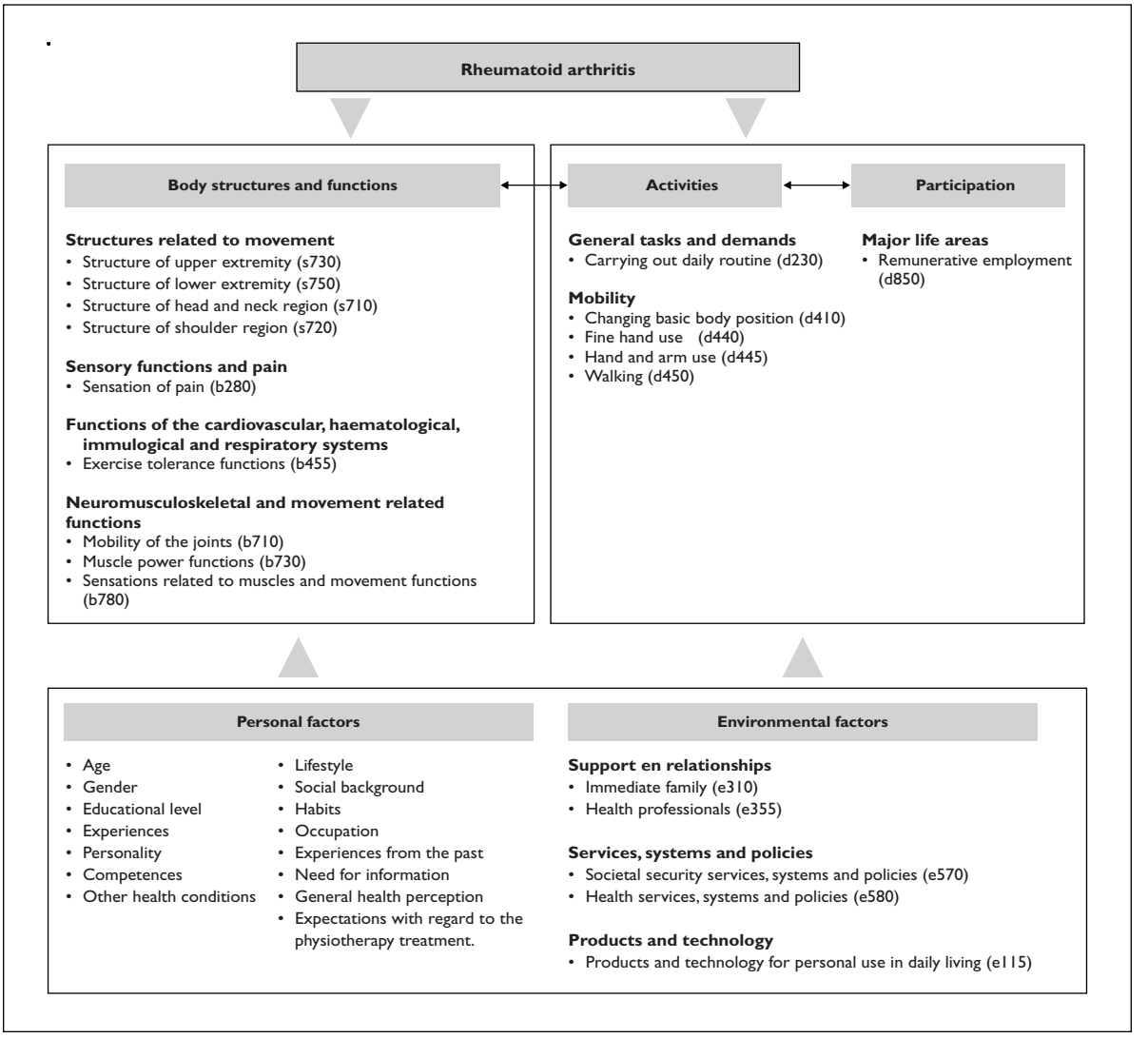

Figure 2. Overview of the most relevant health problems in RA according to the International Classification of Functioning, Disability and Health (ICF) Core Set for Rheumatoid Arthritis (short version).

setting is a shared process between the physiotherapist and the patient. In terms of the ICF, goals are defined within the components of functioning (activities and participation, and body functions and body structures). Goals should be formulated according to the SMART principles (specific, measurable, achievable, realistic, and timely), for example: being able to walk 300 meters (from home to the supermarket and back) two times a week in six weeks. In the next step, specific treatment modalities should be assigned to the treatment goals.

Therapeutic process

With respect to the literature search concerning the therapeutic process, 7 systematic reviews (concerning 33 randomized controlled trials (RCTs)), 4 RCTs and 1 clinical controlled trial (CCT) (published after these reviews) were selected[26-44] (Table 2).

Clinical question 4: Which physical therapy interventions should or should not be given in patients with RA?

RECOMMENDATION 4:
Exercise therapy (in particular exercises with sufficient intensity to improve aerobic capacity and/or muscle strength) should be applied in the physiotherapy treatment of RA patients (level 1).

Table II. Overview of formulated recommendations for the physiotherapy management of patients with RA

Recommendations Diagnostic Process			
Initial assessment		The physiotherapist should assess the patient's health status primarily in terms of activity limitations and participation restrictions. In addition, the therapist may also assess impairments of body functions and structures, as well as personal and environmental factors, insofar as these relate to the limitations and restrictions.	Level 4
Red flags		Physiotherapists should evaluate the presence of "red flags" and points of attention (see figure 2).	Level 4
Treatment plan		Based on the information obtained in the initial assessment, the physiotherapist should define the overall objective and the therapeutic goals while keeping in mind the patient's motivation and the presence of favorable and unfavorable factors.	Level 4
Recommendations Therapeutic Process			
Exercise therapy	Systematic review (8 RCTs) (A1)	On the basis of currently available evidence and best practice, exercise therapy (in particular high intensive exercises) is recommended in RA patients	Level 1 and 4
Education	2 RCTs (both B)	On the basis of currently available evidence and best practice, the guideline development team recommends providing RA patients with information and advice about physical activity	Level 2
The delivery of electric energy	Electrical stimulation: systematic review (1 RCT) (B) TENS: systematic review (3 RCTs) (all B)	Based on the currently available evidence and best practice, the delivery of heat and cold, electric, mechanical and electromagnetic energy, massage, passive mobilization/manipulation and balneotherapy can neither be recommended nor discouraged. In case of high disease activity, the applications which increase the intra-articular joint temperature are advised against. Manual manipulation of the cervical spine is advised against.	Level 2, 3 and 4
The delivery of electromagnetic energy	Systematic review (6 RCTs) (all B)		
The delivery of mechanical energy	Systematic review (2 RCTs) (all B)		
Thermotherapy	Systematic review (7 RCT's) (all B) Extra RCT (B)		
Massage	1 controlled, non--randomized trial (C)		
Manual therapy	1 RCT (C)		
Balneotherapy	Systematic review (6 RCTs) (all B)		
Recommendation Measurements			
Evaluation measurements	Review (A1)	One general measurement instrument should always be used to evaluate the therapeutic goals. Specific evaluations can be done with the help of instruments developed specifically for the relevant joint or extremity. Measurements should preferably be made at the start of treatment and repeated during treatment and at its termination. The selected measurements: the HAQ for functional ability, the VAS for pain and stiffness, EPR-ROM for joint mobility, 6-minute walk-test or Astrand test (incl. Borg) for aerobic capacity and the Hand Held Dynamometer for muscle strength.	Level 1 and 4

RCT: Randomized Controlled Trial; HAQ: Health Assessment Questionnaire

Supervised exercise therapy, aimed at improving muscle strength and/or aerobic capacity, (dynamic exercise therapy) was found to be effective with respect to functional ability, aerobic capacity and muscle strength, and safe in RA patients[26-33] (level 1). The effectiveness and safety of dynamic exercise therapy has also been established in patients with active disease[45] and in patients with early RA[46-51] (level 1). There is a lack of evidence with regard to low to moderate intensity exercise therapy in RA patients.

In previously published international multidisciplinary guidelines and a Dutch multidisciplinary guideline on RA management, exercise therapy[5,6] or dynamic exercise[3,4,7] is recommended. In the physiotherapy guideline on exercise therapy[9] low intensity exercise therapy was recommended, since it was concluded that dynamic exercise therapy might exacerbate the inflammatory process and the risk of damage to the affected joints[9]. The literature on which this guideline was based did however not include a high quality RCT which was published afterwards, showing that dynamic exercise therapy is safe in RA patients with regard to pain and radiological damage[32].

In the Netherlands aerobic exercises and muscle strengthening exercises are usually combined with range of motion (ROM) exercises and functional training (the training of specific daily activities). Exercise therapy is mostly provided on an individual basis in private practices, with few well-defined, individual or group exercise programs for RA patients being available.

In addition to the abovementioned recommendation on exercise therapy, there was overall consensus within the Guideline Steering Committee that exercise therapy should be aimed at patient-specific limitations in activities or participation restrictions and/or impairments of body functions or structures (level 4) and consist of exercises to improve aerobic capacity and muscle strength (level 1) which are, according to the patient's individual health status, combined with range of motion (ROM) exercises, exercises to improve coordination/stability and/or functional training (level 4).

As there is no evidence on the optimal mode of delivery, the Guideline Steering committee could not recommend specific forms of exercise therapy (e.g. land-based or water-based, group or individual basis) and concluded that the mode of delivery would be dependent on the available practice facilities or the patient's preferences (level 4).

RECOMMENDATION 5:

Physiotherapists should provide information and advice on a healthy physical activity level in daily life to patients with RA (level 2).

There is conflicting evidence that in RA patients interventions aimed to become or remain physically active according to the Public Health Recommendations for physical activity (physical activity for 30 minutes in succession on a moderate intensity level on at least 5 days a week) are effective with respect to an increase of the amount of physical activity or improvement of functional ability or quality of life[34,35].

In the Work Group Recommendations of the 2002 Exercise and Physical Activity conference: Session IV, Exercise in the Presence of Rheumatic Disease[52], education of RA patients with regard to physical activity is recommended.

There was overall consensus within the Guideline Steering committee that to optimize RA patients' self-management, education with regard to physical activity in daily life should be recommended as an adjunct to supervised exercises (level 2).

The physiotherapist should also educate the patient about ways to maintain the targets they have achieved during the physiotherapy treatment. Such advice may include tips for maintaining healthy physical activity behaviour in everyday life, or may involve helping the patient take up regular exercise or sports activities or enrol in supervised group exercise programs in the community, for example the "people with arthritis can exercise" (PACE) program[53].

RECOMMENDATION 6:

The provision of heat and cold, electric, mechanical and electromagnetic energy, balneotherapy, massage and manually moving joints can neither be recommended nor discouraged (level 2, 3 and 4).

The application of heat and cold: There is conflicting evidence that the local application of heat or cold is effective in RA patients[36,37] (level 2). Local heat applications have been found to increase the intra-articular temperature of the joint[54] (level 4).

A Dutch multidisciplinary guideline recommends the local application of heat or cold only in individual cases in addition to exercise therapy[7]. The international physiotherapy guideline recommends the use of heat and cold applications[8]. That recommendation is based on two RCTs (one re-

garding cold applications and one regarding the application of heat) whereas in our guideline development we also selected and reviewed five studies with other designs[36], showing less positive results compared to the RCTs. None of the international multidisciplinary guidelines[3-6] included recommendations on the application of heat or cold.

In the Netherlands, heat or cold applications are sometimes used in daily practice as an adjunct to exercise therapy, with the aim to decrease pain or stiffness.

In addition to the abovementioned recommendation on local heat or cold applications, the Guideline Steering Committee advises against the use of local heat application in case of active joint inflammation (level 4).

The application of electrical, mechanic and electromagnetic energy: There is conflicting evidence that ultrasound and TENS are effective in RA patients[39,41] (level 2), whereas there is level 3[38] evidence that the application of electrical energy is effective in RA patients and level 2[40] evidence that low level laser therapy is not effective in RA patients.

In a Dutch multidisciplinary guideline[7] these applications are not recommended. An international physiotherapy guideline[8] recommends the use of therapeutic ultrasound, electrical stimulation, TENS and low-level laser therapy for the management of RA patients.

The Health Council of the Netherlands (Gezondheidsraad) has advised against the use of ultrasound, electrical stimulation, TENS and low-level laser therapy, except for the application of ultrasound in patients with a tennis elbow, TENS in osteoarthritis and low level laser therapy in RA[55]. In the Netherlands, the application of ultrasound, electrical stimulation and low-level laser therapy is not common in the physiotherapy treatment of RA patients. TENS is occasionally used, in case of local joint pain.

In addition to the abovementioned recommendation, the Guideline Steering Committee advises against the use of low-level laser therapy in case of active joint inflammation, as this intervention may increase the intra-articular temperature (level 4).

Massage: There is insufficient evidence that massage is effective in RA patients[42] (level 4). In a Dutch multidisciplinary guideline for RA[7] massage was not recommended. In all other international multidisciplinary and monodisciplinary physiotherapy guidelines[3-6,8,9] massage was not included. In the Netherlands, massage is not commonly applied in the physiotherapy treatment of RA patients (level 4).

Manually moving joints (mobilization/manipulation): There is insufficient evidence that passive mobilization is effective in RA patients[43] (level 4). No recommendations with regard to passive mobilization / manipulation have been formulated in currently available multidisciplinary and physiotherapy guidelines[3-9]. According to the Guideline Steering Committee, some RA patients with a limited joint range of motion of peripheral joints may benefit from passive mobilization (level 4).

In addition to the abovementioned recommendation, the Guideline Steering Committee considered short-term passive mobilization useful in individual cases, provided that it is combined with active exercises.

Passive manipulation of the cervical spine in RA patients may have potential adverse effects due to possible cervical spine instability and is therefore advised against[56] (level 4).

Balneotherapy: Balneotherapy implies bathing in water, particularly from natural mineral and thermal springs, at the optimal temperature ranges between 34 and 35 Celsius and a duration of about 20 minutes[57]. Balneotherapy is commonly used in Europe, but not in North America. Based on the available evidence it is likely that balneotherapy, in combination with exercises, is effective in RA patients[44] (level 2).

In a multidisciplinary guideline for RA[7] balneotherapy as monotherapy was neither recommended nor discouraged. In all other international multidisciplinary or physiotherapy guidelines[3-6,8,9] balneotherapy was not included.

In daily practice balneotherapy is mostly used in health resorts, and provided in combination with other interventions such as exercise therapy. Balneotherapy is covered by multiple health insurance companies. The Guideline Steering Committee found that individual RA patients may benefit from balneotherapy, although it remains unclear to what extent the perceived benefits are caused by the relaxing environment. It was agreed that in case balneotherapy would be used, it should be combined with exercise therapy (level 4).

Evaluation process

With respect to the literature search on evaluation

instruments[3] a journal supplement[58] and three systematic reviews[59] were selected. Evaluation instruments were, similar to the description of the patient's health status and treatment goals, classified according to het ICF.

Clinical question 5: Which measurement instruments should be used to evaluate treatment?

RECOMMENDATION 7:
A general measurement instrument on the level of activities and participation should always be used. In addition, measurement instruments on the level of body functions and structures can be included. Measurements should preferably be done at the start of treatment and repeated during treatment and at its termination (level 1 and 4).

Activities and participation:
The *Health Assessment Questionnaire* (HAQ) is a self-reported, disease-specific questionnaire. The questionnaire consists of 20 questions divided over eight dimensions.

For each of these questions there are four possible responses: score 0 "without any difficulty" to score 3 "unable to do". The highest scores of each of the eight dimensions are added up and divided by eight, resulting in a total score ranging between 0 and 3[60].

Body functions and structures:
A Visual Analog Scale (VAS) for pain and morning stiffness[59] is usually a horizontal line of 100 millimeters, without a scale division, with on the left end "no pain or morning stiffness" and on the right end "maximal (unbearable) pain or morning stiffness". By means of a vertical line, the patients express how much pain or morning stiffness they experienced during the last week. The VAS score is determined by measuring the distance in millimeters from the left end of the line to the point that the patient marks.

For measuring *muscle strength,* the Hand Held Dynamometer was recommended[59]. The Hand-Held Dynamometer is suitable for measuring muscle strength of almost all clinically relevant muscles (as well in the upper extremities as in lower extremities).

For measuring *aerobic capacity,* the 6-minutes walk test or the sub maximal bicycle test (including the Borg Scale) were recommended. During the 6-minutes walk test the patients have to walk 6 minutes at a self chosen walking speed and they have to try to overcome as much distance as possible, without running. The accomplished distance is the total distance at the end of the 6 minutes[59]. In case a walking test is not possible, for example because of severe joint problems, the aerobic capacity can be measured by performing a bicycle test, for example the Ästrand test[61]. The Borg scale is a subjective scale for rating the perceived exertion (RPE) on a scale of 6 to 20[25].

For measuring joint mobility the *Escola Paulista de Medicina–Range of Motion scale (EPM-ROM)* was recommended. The EPM-ROM measures the mobility of ten different joints at each side of the body (elbows, wrists, thumps, fingers, hips, knees and ankles) using a goniometer. The joint mobility of every joint is scored from 0 "whole movement is possible" to 3 "severely limited". The scores of the included joints are added up, resulting in a total score ranging from 0 to 30[62].

Discussion

This study describes the development of a comprehensive physiotherapy guideline for the management of RA. This guideline is based on recent evidence and expert opinion. It was developed according to standardised procedures for formulating recommendations. All elements were described according to the ICF and the ICF Core Set for RA.

With respect to physiotherapy guidelines in RA, at present only the Ottawa Panel guidelines are available, which were published in 2004[8,9]. Whereas the Ottawa Panel guidelines include only the therapeutic process, the present guideline also comprises recommendations on the diagnostic and evaluation process. Concerning interventions, the Ottawa Panel includes recommendations on exercise therapy, thermotherapy and electrotherapy, whereas the present guideline comprises recommendations on exercise therapy, education with regard to physical activity, the application of electrical, mechanic and electromagnetic energy, thermotherapy, balneotherapy, massage and mobilization/manipulation.

A comparison of the contents of the recommendations on the interventions that the Ottawa Panel guidelines and the present guideline have in common shows some discrepancies. In the Ottawa guideline exercise therapy with low/moderate

intensity was recommended, since dynamic exercise therapy was regarded not to be safe in RA patients, whereas in the present guideline exercise therapy with a high intensity was recommended. This difference is likely to be due to the year of publication. After the publication of the Ottawa Panel guideline, a good quality RCT with sufficient power was published, showing that dynamic exercise therapy does not increase disease activity or radiological damage in RA patients[32].

In the Ottawa Panel guideline both thermotherapy and electrotherapy were recommended, whereas in the current guideline these interventions were neither recommended nor discouraged. This difference may be related to a number of factors, including the year of publication, differences in the inclusion and exclusion criteria used for the literature review and different outcomes of expert opinion. After the publication of the Ottawa Panel guideline in 2004, a new study with regard to thermotherapy was published[37] and the review with regard to low level laser therapy was updated[40]. In the first study with regard to thermotherapy (specifically cold applications) various adverse effects were found. In the second updated review more trials were included which showed that thermotherapy is not effective. Furthermore, the Ottawa Panel used very strict inclusion and exclusion criteria and therefore included only a small number of RCTs (2 on thermotherapy and 9 on electrotherapy). In the present guideline various study designs, also other than RCTs, were included. Overall, these additional studies showed more negative outcomes. In the process of guideline development, expert opinion is also involved. In the Netherlands various interventions, such as low level laser therapy, are not commonly applied and were not considered effective by the experts. All these differences have lead to different, less positive, recommendations.

Concerning the comparison of the recommendations in the present guideline with those in multidisciplinary guidelines and sets of recommendations on comprehensive RA management[3-7] it appears that the recommendations on exercise therapy are similar, with dynamic exercises being recommended in ACR[3], EULAR[4] and BSR[5] guidelines. With respect to TENS and thermotherapy, the BSR guidelines recommend their usage[5], whereas in the present guideline these applications are neither recommended nor advised against. As the conclusions from the literature are similar in both the BSR guidelines and the present guideline, namely that there is conflicting evidence and/or no evidence for the effectiveness of these interventions, it appears that expert opinion varied.

For all other interventions, there were no recommendations available for comparison in multidisciplinary guidelines.

To facilitate the use of guidelines in daily practice it is important to apply an implementation strategy. So far, it is unclear to what extent the Ottawa Panel physiotherapy guidelines for the management of RA patients have been implemented and if so, which strategy was applied. Implementation studies with regard to other guidelines have shown that didactic education and passive dissemination strategies were ineffective implementation strategies[66]. Multifaceted interventions, interactive education and clinical reminder systems have been shown to be effective implementation strategies for physiotherapy guidelines, including guidelines for low back pain and whiplash[67]. The implementation strategy of this Dutch RA physiotherapy guideline included dissemination through regular mail, publication on a website and regional organized educational sessions.

More research is needed to determine the level of guideline adherence, the extent to which the use of guidelines improves patient outcomes and leads to a more time- and cost-effective physiotherapy management.

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THE INTRIGUING CO-EXISTENCE OF A CHRONIC PERIAORTITIS, A PERICARDITIS AND A PANCREATITIS: CASE REPORT

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Lina Carvalho**, Correia Xavier***, José Nascimento Costa****

Abstract

Chronic periaortitis (CP) refers to a spectrum of diseases whose common denominator is a fibro-inflammatory tissue developing in the periaortic space and frequently encasing surrounding structures like the kidney and ureters. There is no unified concept regarding the primary aetiology of CP, but recent studies have demonstrated that CP may present features of auto-immune diseases. CP involves three main entities, namely idiopathic retroperitoneal fibrosis (IRF), inflammatory aneurysms of the abdominal aorta (IAAAs) and perianeurysmal retroperitoneal fibrosis (PRF). These entities are usually diagnosed using computed tomography or magnetic resonance imaging, which typically show a retroperitoneal mass surrounding the aorta and that extends laterally without displacing it. Positron emission tomography is useful for the full assessment of the extent of the disease and its metabolic activity. The inflammatory and chronic relapsing nature of these diseases compels the use of medical therapy, which is based on high--dose steroids with a tapering scheme combined with immunosuppressive agents in refractory or relapsing disease. The authors report the clinical and radiological characteristics of a nonaneurysmatic form of chronic periaortitis in a woman presented with pericarditis, pericardial effusion and a pancreatitis. They also describe the investigation and management of this unusual condition

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Keywords*:* Chronic periaortitis; Retroperitoneal Fibrosis; Vasculitis; Pericarditis; Autoimmune Pancreatitis.

Introduction

Chronic periaortitis (CP) is an uncommon disease characterised by the presence of a fibro-inflammatory mass surrounding large-vessels like aorta and the iliac arteries and extending into the retroperitoneum, in which often entraps some of the surrounding structures, like the ureters and inferior vena cava[1,2]. CP includes a spectrum of idiopathic diseases: idiopathic retroperitoneal fibrosis (IRF), inflammatory aneurysms of the abdominal aorta and perianeurysmal retroperitoneal fibrosis[2,3]. However, the most accepted definition is the classification of CP in two forms: the *aneurysmal* form (dilated aorta) and the *non-aneurysmal* one.

Regarding the pathogenesis of CP, there is no unified concept. Initially, the leading theory was that CP was a localized inflammatory reaction against antigens in the atherosclerotic plaques of the aorta[3,4]. However, some recent studies have demonstrated a strong association between CP and HLA-DRB1*03, which is a marker of auto-immunity, being linked to prototypical autoimmune conditions such as type 1 diabetes, myasthenia gravis and auto-immune thyroiditis[5].

Some similarities can also be found in CP and a number of chronic inflammatory/autoimmune conditions that diffusely affect the aorta and its branches and are generically referred as aortitis[6,7]. Finally, the hypothesis that some cases of CP (particularly the non-aneurysmal forms) are part of a newly recognized clinic-pathological systemic disease, called IgG4-related systemic disease (IGG4--RSD), is sustained by recent works[6,8]. IgG4-RSD is characterized by increased serum IgG4 concentra-

tions and IgG4-expressing plasma cells diffusely infiltrating organs throughout the body[8,9,10].

CP is characterized by non-specific signs and symptoms related to the mechanic and compressive effects of the retroperitoneal mass on the adjacent structures, such as back or abdominal pain, normally described as insidious, persistent and dull, constipation, deep vein thrombosis, leg edema, varicocele or hydrocele[2,11,12-14].

Constitutional symptoms such as fever and weight loss may occur in the early stages. Laboratory investigation often shows increased acute-phase reactants, accompanied by normocytic anaemia, leukocytosis and hypoalbuminaemia[2]. Autoantibodies (particularly antinuclear antibodies) are positive in a varying proportion of the cases, but with no clinical correlation. The positivity of anti-neutrophil cytoplasmic antibodies, rheumatoid factor and antibodies against smooth muscle cells and thyroglobulin may indicate an associated auto-immune disorder [2,15,16].

Because the presentation symptoms are often non-specific, in the presence of CP and retroperitoneal fibrosis, secondary causes such as drugs, infections and malignancies should be first excluded[17-19].

The "gold-standard" imaging techniques used in the diagnosis and characterization of CP are: contrast-enhanced computed tomography (CT) scanning and magnetic resonance imaging (MRI)[18-21]. In the last years the ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) has been used for assessing the metabolic activity of the periaortic inflammatory tissue[18].

The histology of the inflammatory periaortic tissue normally shows fibrosis with signs of active mononuclear cell inflammation[6,17]. This inflammatory infiltrate mainly consist of T and B lymphocytes, plasma cells and macrophages, although scattered eosinophils can also be found interspersed between collagen bundles and sclerosis.

The initial clinical approach to these patients should rule out all the potential factors (i.e.: drugs, infections) that may exacerbate this disease. Steroids are considered the first choice option in medical treatment. The initial dose is 1mg/Kg/day and treatment decisions related to the degree of dose reduction must be individualized and based on clinical and radiological response. Besides steroids there are some immunosuppressive drugs, for instance methrotexate, azathioprine, cyclophosphamide, mycophenolate mofetil that have been used as steroid sparing agents or in those cases not responding the initial steroid treatment[9,19,22-24]. Other drugs with different mechanisms of action, such as tamoxifen[23] and colchicine[24] have been used as adjuvant in steroid treatment cases.

Long-term follow-up is recommended in all patients and given to the array of therapeutic agents available it's possible a therapeutic approach capable of controlling the disease course that allows a sustained long-lasting remission.

Case report

The authors report the case of a 71-year-old caucasian woman presented to the emergency department with a three-month-history of progressive shortness of breath, left side chest pain and left side flank pain. She also referred anorexia, 4 Kg weight loss and malaise in the previous months. The patient denied nausea, vomiting and diarrhoea. She had a past medical history of a strong cardiovascular disease with a myocardial infarction, in 2004, four coronary-stents and hypertension. Her usual medication was: bisoprolol 5mg/ /day; aspirin 100mg/day, pravastatine 40mg/day, telmisartan plus hydroclorotiazide (40mg + 12.5 mg) and sertraline 50mg/day. On the initial clinical evaluation the patient was in distress, febrile (38.2ºC), hypotensive (blood pressure was 91/51 mm Hg), the heart rate was 58 beats per min, the respiratory one was 18 cycles per min and saturation by pulse oximetry O_2 was 89% on room air. Chest auscultation revealed course breathe sounds bilaterally with no crackles. The cardiac auscultatory examination was unremarkable; specifically, there were no audible murmurs, gallops, or rubs. The electrocardiogram (ECG) showed a normal sinus rhythm (rate 60 beats per minute) with low--voltage QRS complexes not present in the previously ECG. Chest radiography presented marked cardiomegaly. Laboratory data revealed normocytic anaemia, hypoalbuminaemia, elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CPR) of 9 mg/dl (normal<0.5mg/dl), amylase was normal and myocardial enzymes were negative. The two-dimensional ecochardiogram detected a large pericardial effusion, but with no diastolic collapse of the right heart chambers. The patient was admitted in the Coronary Care Unit (CCI), where she was submitted to a therapeutic pericar-

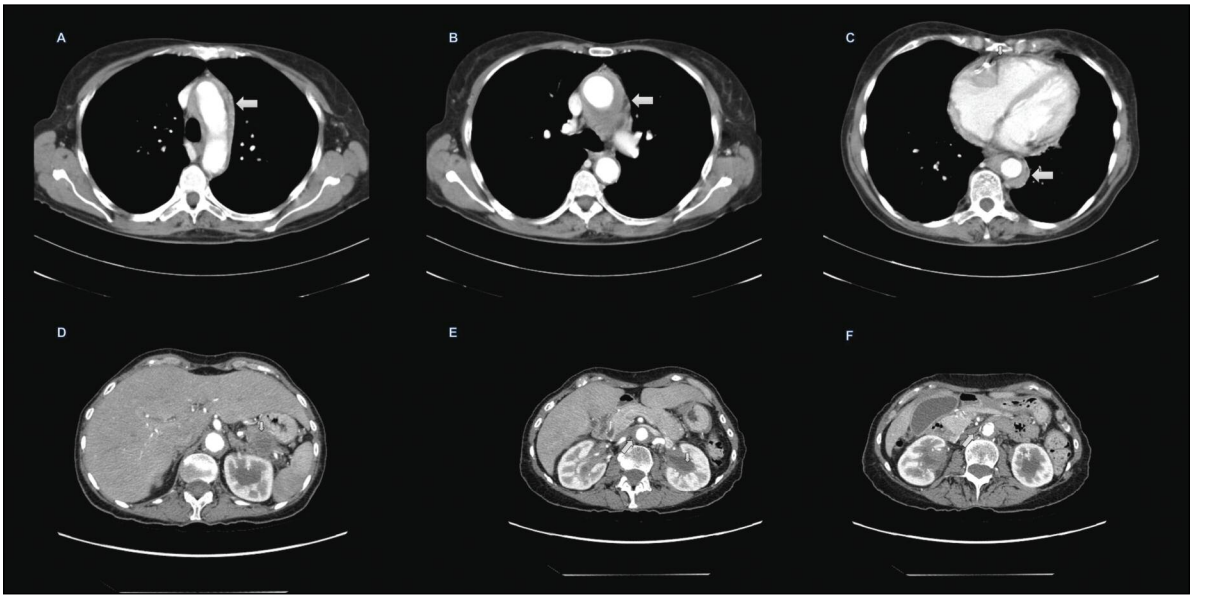

Figure 1. Computed tomography (CT) scan (axial views). **A, B** and **C** (thoracic CT) revealing a non aneurismatical form of periaortitis involving the ascending and descending aorta (big arrows). **D, E** and **F** (abdominal CT) revealing a periaortitis of the aorta (big arrows). It also shows a hypodense and heterogeneous area in the tail of the pancreas (small arrow-image D) and calyceal dilatation (small arrow-image E).

diocentesis. More than 800ml of pericardial fluid was taken. The laboratory workup of the pericardial exudate was negative for neoplastic cells, mycobacterium and other germens. After reaching cardiac stabilization the patient was transferred to the Internal Medicine Ward for a further study. There she was submitted to an abdominal ultrasound because of persistent left flank pain. The abdominal ultrasound showed dilated calyces and thickening of the urothelial wall suggesting an inflammatory process. Subsequently a scintigraphy was done, which excluded ureteric obstruction. Additional laboratory investigation including ANA, ANCA, and serological testing for Coxsackievirus B virus, EBV, CMV, Rubella virus, HSV, parvovirus B19, toxoplasmosis, HIV, hepatitis B and syphilis were negative. The serum proteinogram was normal with normal serum IgG4 concentration. A thoracic and abdominal CT scan (Figure 1) and MRI (Figure 2) were done. They revealed a soft tissue mass embracing the thoracic aorta and spreading down to the abdominal aorta without any abnormal aorta dilatation (Figures 1 and 2). Both exams confirmed the thickening of the ureteral wall and also revealed a hypodense and heterogeneous area in the tail of the pancreas. A positron emission tomography (PET) was undertaken to better characterize the soft tissue surrounding the aorta and the hypodense area in the tail of the pancreas. This exam showed the hypermetabolic process embracing the thoracic and abdominal aorta, with the same metabolic pattern in the body and tail of the pancreas (Figure 3). This last finding in the pancreas was suggestive of an inflammatory process, which is characteristic in pancreatitis.

This case was discussed with the surgeons, because a tissue biopsy was needed not only to confirm the diagnosis of a CP, but also to exclude other diseases such as neoplasia or infections. Since the surgical approach of the pancreas was considered by the surgeons a complicated procedure, a percutaneous pericardial and periaortic soft tissue biopsy of the inflammatory mass, using a mediastinal window, was done. The histopathology revealed an inflammatory tissue with a lymphoplasmocytic infiltration, areas of fibrinoid necrosis and small-vessel vasculitis (Figure 4), which confirmed the diagnosis of chronic periaortitis confined to the thoracic and abdominal aorta and idiopathic retroperitoneal fibrosis. The patient began treatment with an initial dose of 60mg/day of methylprednisolone and 1mg/day of colchicine. The β-blocker was stopped. After the first month treatment a rapid clinical improvement was observed. The 3-month follow-up thoracic and abdominal CT scan showed mild regression in the in-

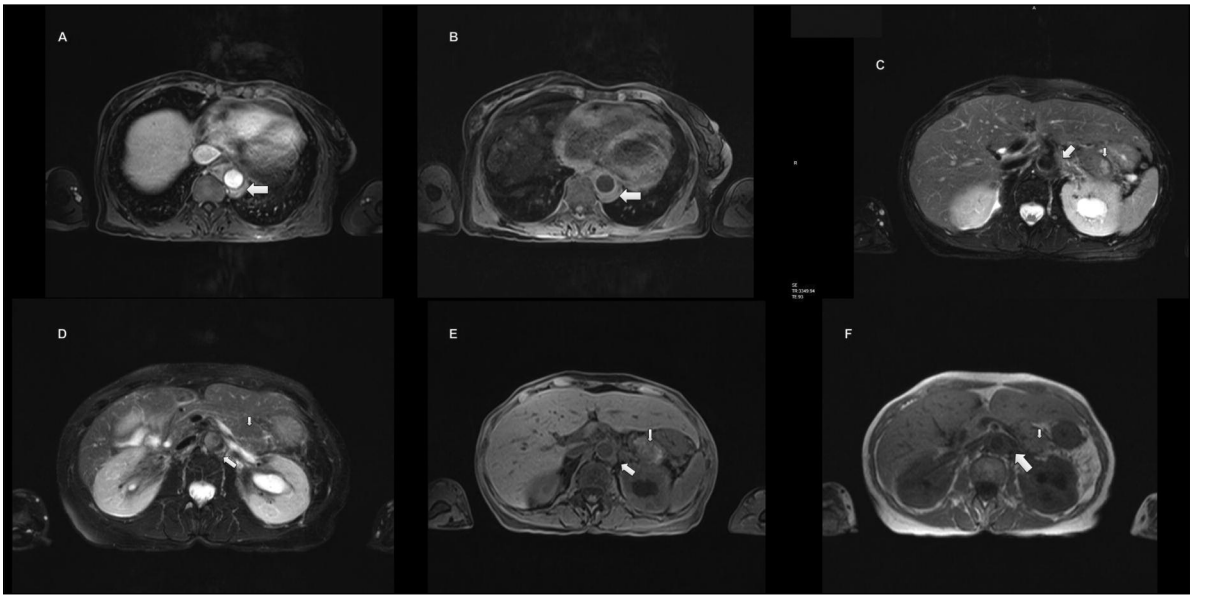

Figure 2. Magnetic Resonance imaging (MRI). **A** and **B** (thoracic axial view). The T1 (**A**) and T2 (**B**) weighted images reveal an intermediate intensity signal in the periaortic tissue. Image **C** (T2 weighted abdominal axial views) reveal hyperintense signal in the periaortic tissue (big arrow) and in the tail of the pancreas (small arrow). **D, E** and **F** (different sequences of T1 weighted images axial views) revealing an intermediate signal in the periaortic tissue (big arrow) and an intermediate and heterogeneous signal in the tail of the pancreas (small arrow).

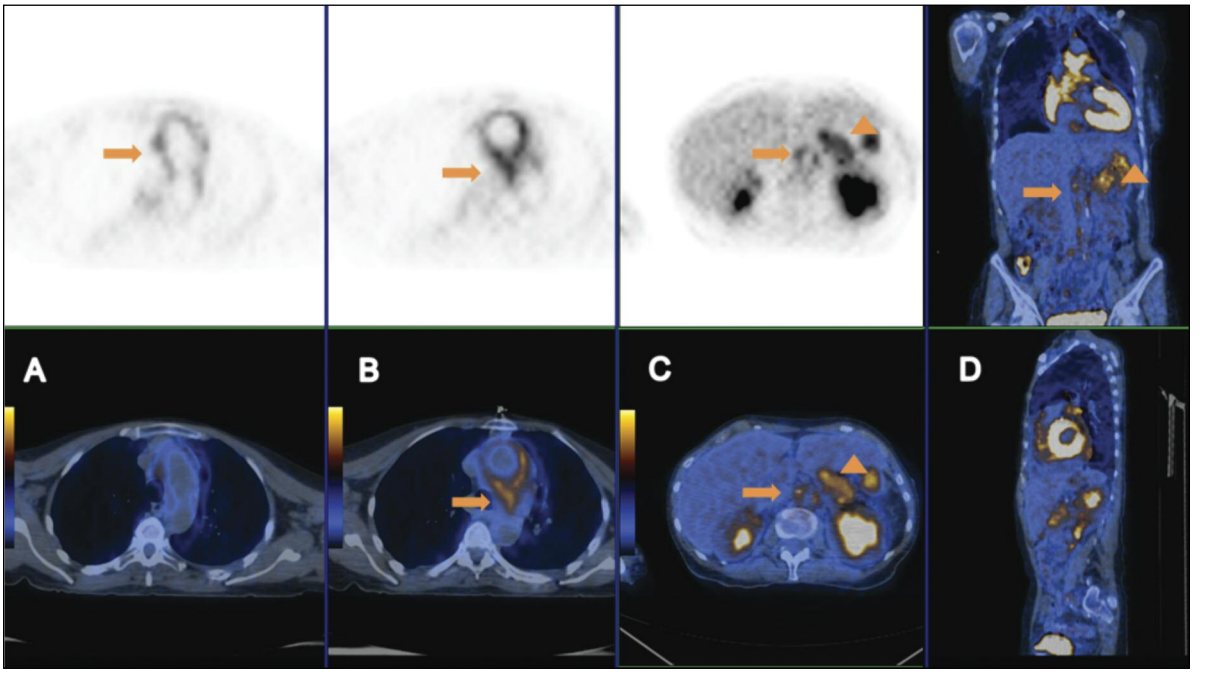

Figure 3. F18-Fluordeoxyglucose (FDG) positive emission tomography. Images **A, B** and **C** (axial views) showing increased tracer uptake in the tissue surrounding the ascending aorta and the abdominal aorta (arrow). There is also an increased heterogeneous tracer uptake in the body and tail of the pancreas, suggestive of a pancreatitis (arrowhead). Image **D** (coronal and sagittal views) showing increased uptake in the ascending aorta and a segmented uptake in the abdominal aorta (big arrow) and in the body of the pancreas suggestive of a pancreatitis (arrowhead).

flammatory tissue in the aorta wall, and the evolution into a pseudocyst of the hypodense and heterogeneous area in the pancreas (Figure 5). A 3-month follow-up echocardiogram was also done and showed no residual pericardial effusion. The patient has had regular follow-ups and after an 8-month-treatment she is now on a maintenance dose of 8mg/day of methylprednisolone and 1mg/day colchicine.

Discussion

Chronic periaortitis is an uncommon fibro-inflammatory disorder of the aorta characterized by a perivascular fibrotic tissue that may spread into the retroperitoneum encasing the ureters and other structures. This patient had a nonaneurysmal form of a chronic periaortitis that extended caudally from the thoracic to the abdominal aorta and retroperitoneum. The chronicity of this inflammatory process was based not only on the radiologic findings, but also on the constitutional symptoms, the elevated acute-phase reactant levels and negative serologic tests presented in this patient for months. The diagnosis of CP and retroperitoneal fibrosis was initially suggested based on the CT, RMN and FDG-PET findings, which were

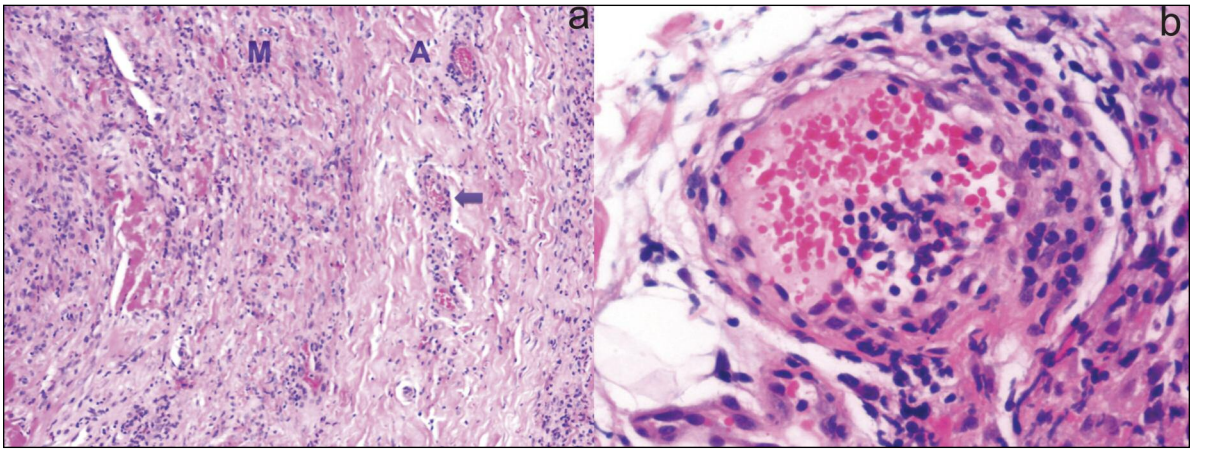

Figure 4. A. Periaortitis – lymphoid cells and plasma cells invade adventitia (A) and dissociate medial layer (M). Vasa vasorum are involved with vasculitis phenomena (arrow). HE X 100. **B.** Small vessel vasculitis revealed by lymphocytes, plasma cells and eosinophils in the endothelium. HE X 400

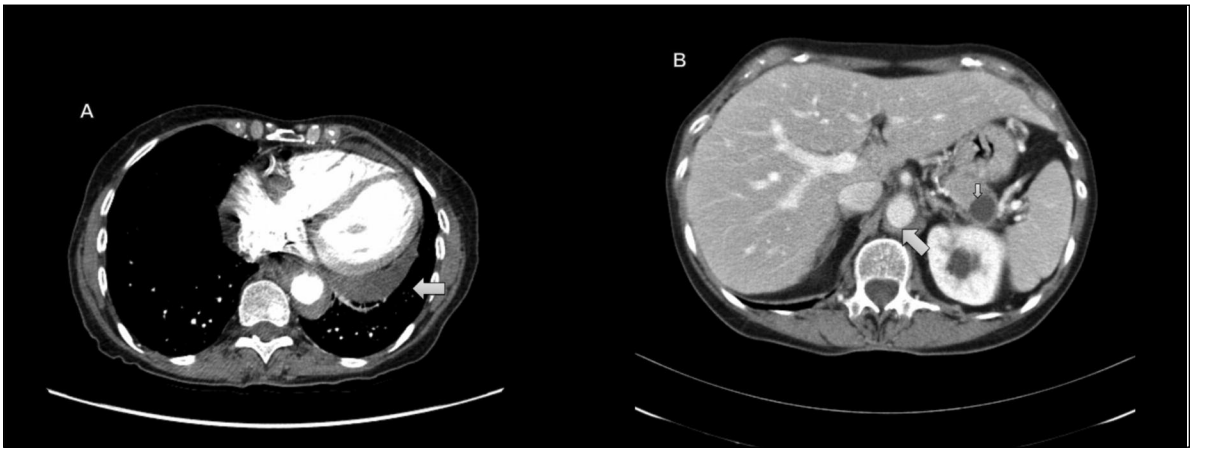

Figure 5. A. Three months follow-up CT scan of the chronic periaortitis. **A.** (Thoracic axial view) regression of the periaortic thoracic mass and of the pericardial effusion (arrow). **B.** (Abdominal axial view) regression of the inflammatory periaortic tissue (big arrow) and the evolution into a cyst of the initial hypodense area in the body and tail of the pancreas (pancreatitis)(small arrow).

done when searching for a neoplasm because of the initial presentation of a pericarditis with pericardial effusion. The histological analysis of the periaortic and pericardial tissue confirmed the diagnosis of a CP. The FDG-PET revealed the same metabolic pattern in the periaortic tissue and in the body and tail of pancreas, which was suggestive of an inflammatory process, such as pancreatitis. The 3-month follow-up thoracic and abdominal CT scan revealed a mild regression of the inflammatory tissue embracing the aorta, reduction of the ureteric wall thickening, resolution of the pericardial effusion and the evolution into a pseudocyst of the hypodense area in the pancreas. These last findings supported the hypothesis that the pericarditis and the pancreatitis were in relation with an abnormal extension of the inflammatory periaortic process. The hypothesis that these findings could be related to the newly recognized IgG4-related systemic disease was also considered, since this disorder may manifest as thoracic aortitis or retroperitoneal fibrosis[8]. This disorder was first recognized to involve the pancreas as autoimmune pancreatitis and is now known to involve other organs[8,15]. Therefore, IgG4 related systemic disease should always be considered in any patient found to have periaortitis or retroperitoneal fibrosis. Since our patient had normal serum IgG4 concentration and no histological features characterized by the presence of IgG4-expressing plasma cells, the diagnosis of an IgG4-related periaortitis and pancreatitis was ruled out. As a biopsy of pancreatic hypodense area was not performed, because of the difficult technical approach, there is no histological result that could document the diagnosis of a pancreatitis of possible autoimmune origin, only the evidence of radiological improvement. The successful medical treatment spared the patient an unnecessary surgical approach of the initial hypodense area in the pancreas.

In this case we didn't use MRI for the radiological follow up, instead we preferred CT, since the risk (even though the patient didn't have chronic renal disease) of developing Gadolinium related Nephrogenic Systemic Fibrosis might exist in this patient with an already inflammatory-fibrosing disease. The strong cardiovascular background of this patient sustains the original theory that CP and IRF are a result of a local reaction to advanced Atherosclerosis. Though the patient didn't have any history suggestive of an underlying autoimmune disease, the histological findings, such as lymphoplasmocytic infiltration, suggestive of small-vessel vasculitis support the hypothesis that CP is related to an inflammatory/autoimmune systemic disease. Currently, there is no standardized treatment for CP and IRF. Therapeutic options vary from steroids to other immunosuppressive drugs. The promising results of some studies[25] prompted the initiation of methylprednisolone and colchicine in this patient. Other effective treatments options were available, such as tamoxifen with less long-term hazardous side-effects[23]. However, because of the clear clinical and radiological improvement, the patient is being maintained on the same treatment with steroids (with slower reduction in the dose) and colchicine.

This case report illustrates the importance of the awareness and recognition of imaging findings that are crucial for an early diagnosis and institution of adequate therapy. It is also an example of an atypical presentation of a CP and IRF and calls attention for the rare association with a pericarditis and a pancreatitis.

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METOTREXATO NO TRATAMENTO DA SÍNDROME SAPHO COMPLICADA POR QUELÓIDES

Azevedo VF*, Dal Pizzol VI**, Lopes H***, Coelho SP***, Czeczko LEA****

Resumo

A síndrome SAPHO é uma entidade clínica pouco comum, de definição recente na literatura médica, que afeta tipicamente crianças, adultos jovens ou indivíduos de meia idade. Caracteriza-se pela associação de lesões de pele (acne, pustulose palmoplantar ou hidradenite supurativa) com sinovite, hiperostose e osteíte, não havendo obrigatoriedade de todas as manifestações simultaneamente.

Relatamos o caso de um homem, atualmente com 42 anos, que iniciou acompanhamento no HC/UFPR em 1992 por presença de acne extenso. Tinha recebido vários diagnósticos ao longo dos anos e passou por vários cursos de antibioterapia, tentando controlar lesões pustulosas e de hidradenite. Estas lesões evoluiam com cicatrizes hipertróficas, sendo submetido, inclusivé, a zetaplastia na nuca por limitação da mobilidade do pescoço. Em 1996 foi iniciada isotretinoína com boa resposta, porém houve retorno das lesões purulentas após finalizado o tratamento. Dez anos depois, foi tentado mais um ciclo de isotretinoína em outro serviço, quando apresentou artrite em membros superiores e inferiores, emagrecimento de 11kg em 3 meses e VHS de 131 mm na 1ª hora. Foi então diagnosticado como síndrome SAPHO e iniciado metotrexato 10 mg por semana, com melhoria inicial expressiva. Ao longo da sua evolução, teve exacerbações articulares e cutâneas, porém atualmente mantém-se estável com 20 mg de metotrexato por semana e 5 mg de finasterida ao dia.

A síndrome SAPHO é uma doença rara, muitas vezes com diagnóstico difícil e tardio. As lesões de pele deste paciente precederam em muitos anos as lesões articulares e mostraram-se um verdadeiro desafio terapêutico, tendo melhorado significativamente após a introdução do metotrexato. Embora a doença cutânea tenha sido complicada por desenvolvimento de cicatrizes hipertróficas houve excelente resposta ao tratamento sem desenvolvimento de outras sequelas.

Palavras-chave: SAPHO; Metotrexato; Acne conglobata; Quelóide.

Abstract

SAPHO syndrome is an uncommon clinical entity, recently described in literature, which usually affects children, young adults and middle-aged people. It is defined by the association of skin lesions (severe acne, palmo-plantar pustulosis, supurative hidradenitis), synovitis, hiperosthosis and osteitis; however, not all manifestations are required for correct diagnosis.

We report a currently forty-two year-old man who initiated follow-up in 1992 for severe acne. His diagnosis changed along the years and has been treated with antibiotics many times to control pustule formation and hidrosadenitis, which evolved to keloidal scars, requiring neck zethaplasty due to limitation of mobility. In 1996 isotretinoin was started, with good response to treatment but recurrence after its completion. Ten years later, isotretionoin was being used again due to worsening clinical picture when the patient developed polyarthritis, lost 11kg in 3 months and was found to have an elevated erythrocyte sedimentation rate. SAPHO syndrome was then diagnosed by the Rheumatology clinic, which started methotrexate at 10mg per week to a good clinical response. Several cutaneous and articular flares have occurred since, however he is now clinically stable with methotrexate 20mg per week and finasteride 5mg per day.

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SAPHO syndrome is a rare disease and its diagnosis is often late and difficult. In this case, skin lesions preceded arthritis in several years and have been resistant to other common treatments. The patient had a better improve after initiation of methotrexate. Although the skin disease has evolved to keloids, the patient has had excellent treatment response.

Keywords: SAPHO; Methotrexate; Acne conglobata; Keloids.

Introdução

A síndrome SAPHO, cujo nome é um acrónimo cunhado em 1987 para a associação de sinovite, acne, pustulose palmo-plantar, hiperostose e osteíte[1], é uma entidade clínica pouco comum e pouco conhecida fora da especialidade de reumatologia. Para o diagnóstico desta enfermidade, não é obrigatório a presença simultânea de todas estas alterações, que podem inclusivé ocorrer em momentos diferentes da evolução clínica do paciente.

Tipicamente, a síndrome afeta crianças, adolescentes e adultos jovens, podendo ocorrer também em adultos de meia idade. O seu tratamento envolve o uso de diversos agentes de acordo com as manifestações presentes da doença, sendo utilizados antiinflamatórios, bifosfonatos, corticóides, imunomoduladores e isotretinoína, conforme a predominância de manifestações clínicas (ósseas, articulares ou cutâneas)[2-5]. Além disso, várias especialidades podem ser envolvidas no tratamento, como ocorreu no caso do paciente que apresentamos.

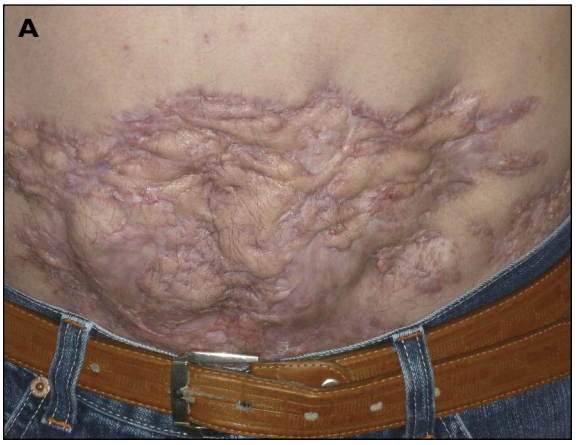
Caso Clínico

Relatamos o caso de um paciente do sexo masculino, atualmente com 42 anos, que iniciou acompanhamento no Serviço de Dermatologia do Hospital de Clínicas da Universidade Federal do Paraná (HC-UFPR) em 1992 por um quadro de lesões pustulosas da pele 2 anos antes. Com o diagnóstico inicial de escrofuloderma, foi tratado com sulfametoxazol e trimetoprim, sem melhoria. A biopsia de pele apresentava inflamação crónica de padrão tuberculóide, o que levou à suspeita de tuberculose, cuja investigação foi negativa, além de tratamento empírico, sem melhoria. Em 1996, foi submetido a exérese de hidradenite e definido o diagnóstico de acne conglobata, sendo tratado com isotretinoína, com a qual houve uma melhoria inicial expressiva das lesões, mas que voltaram a aparecer no final do tratamento em menor quantidade e sempre com alguns focos purulentos, sendo submetido a antibioterapia com sulfametoxazol e trimetoprim e tetraciclina. Devido ao padrão de cicatrização fibrosante das pústulas, com cicatrizes hipertróficas e quelóides, condicionando limitação da mobilidade do pescoço, foi submetido a zetaplastia em 1998 pelo Serviço de Cirurgia Geral do HC-UFPR.

As lesões de pele mantiveram-se estáveis até 2004, quando houve novamente agravamento do quadro, questionando-se então o diagnóstico de acne conglobata. Foi considerado, nesta altura, o diagnóstico de síndrome de hiperqueratose folicular com infecção secundária e feito novo ciclo de antibioterapia. A resposta ao sulfametoxazol e trimetoprim foi má, pelo que se optou por um novo ciclo de isotretinoína, iniciada em dezembro de 2005, desta vez com melhoria das lesões. A isotretinoína foi suspensa em abril de 2006, quando o paciente apresentou omalgia bilateral, emagrecimento, anorexia e tumefacção articular, sendo solicitado avaliação ao Serviço de Reumatologia.

Nessa altura, o paciente apresentava artrite dos ombros, cotovelos, punhos, interfalângicas distais e proximais de mãos, joelhos e tíbio-társicas, associado a emagrecimento de 11kg em 3 meses e VS elevada – 131 mm na primeira hora. Na investigação complementar a radiografia da bacia não apresentava sacroiliíte e o doente era HLA-B27 negativo. Fez-se então o diagnóstico de síndrome SAPHO e iniciou-se tratamento com metotrexato 10 mg semanal e diclofenac para tratamento da poliartrite (já usava finasterida 5 mg ao dia, prescrito pela Dermatologia). Evoluiu com boa resposta, porém lenta, das lesões de pele, do quadro articular e dos parâmetros inflamatórios. Teve exacerbações esporádicas do quadro cutâneo, sendo feito nova antibioterapia. Em 2009 apresentou novo agravamento do quadro articular, necessitando de aumento progressivo da dose do metotrexato para 15mg e posteriormente 20mg semanais para controle. As tentativas de parar a finasterida não obtiveram sucesso, necessitando sua manutenção continua até hoje. No momento, o paciente encontra-se estável, sem novas lesões de pele ou articulares, com melhora significativa de todo o quadro inicial, porém com cicatrizes extensas devido às lesões crônicas (Figuras 1a e 1b).

Em Junho de 2010 a radiografia da bacia mostrou sinais de sacroiliíte direita.



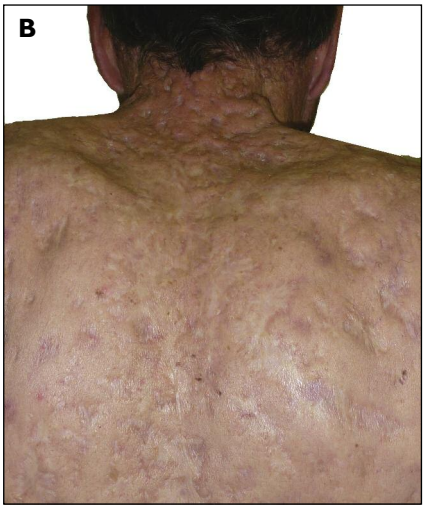


Figura 1a e 1b. Fotos atuais do paciente – destacam-se as áreas extensas de cicatrizes hipertróficas e quelóides

Discussão

Destacam-se neste caso a longa evolução das lesões da pele, com padrão deformante, e a dificuldade do seu controle e diagnóstico. As várias tentativas prévias foram infrutíferas, sempre com recidivas das lesões. Também é digno de nota o longo período de tempo entre as lesões de pele e o aparecimento de sintomas articulares, o que dificultou o diagnóstico da síndrome neste paciente. É comum que ocorra atraso no diagnóstico definitivo, tanto devido à raridade quanto às manifestações pouco usuais da síndrome, havendo relatos nos quais o diagnóstico demorou mais de 10 anos[4].

A descrição inicial da síndrome SAPHO por Chamot *et al* englobava uma série de pacientes com características semelhantes, que na literatura já eram conhecidas por outros nomes como doenças separadas. Chamot agrupou estes casos sob uma denominação comum. Atualmente, a hipótese de síndrome SAPHO deve ser levantada na presença de doença cutânea inflamatória com manifestações osteoarticulares que satisfaçam os seguintes critérios[1,2,6]:

- lesão de pele (acne conglobata, acne fulminans ou hidradenite) em conjunto com lesões osteoarticulares (sinovite, hiperostose ou osteíte)
- pustulose palmo-plantar e lesões osteoarticulares
- osteomielite crónica multifocal recidivante do esqueleto axial ou apendicular com ou sem lesões de pele associadas.

A síndrome SAPHO tem prevalência igual em ambos os sexos, entretanto é relatado uma freqüência maior de pustulose palmo-plantar nas mulheres[4,7] e acne nos homens[4,7] afetados. Cerca de 60% dos pacientes têm envolvimento cutâneo, que se pode apresentar de 2 até 20 anos após as lesões osteoarticulares e, em casos raros, o envolvimento cutâneo pode ser leve. A lesão de pele na síndrome SAPHO é um componente importante do diagnóstico, sendo um dos fatores que pode levar o paciente à consulta. Existem ainda relatos de associação desta síndrome com psoríase, dermatoses neutrofílicas e doenças intestinais inflamatórias, como a retocolite ulcerativa e a doença de Crohn[8-11], devendo o médico estar atento para outras manifestações e associações.

A patogênese da síndrome ainda é desconhecida. A suspeita de um fator causal infeccioso recai sobre a bactéria *Propionibacterium acnes*, já que estudos relatam o seu achado nas lesões articulares de alguns pacientes (tanto na parede torácica anterior como na coluna vertebral e esqueleto apendicular) e o fato da síndrome responder à terapêutica antibiótica crônica em alguns pacientes[5,8,12]. Entretanto, ao contrário de outras espondilartrites, a presença do HLA-B27 é pouco freqüente na síndrome SAPHO, e alguns estudos sugerem uma predisposição genética por *loci* fora do complexo principal de histocompatibilidade (MHC)[12]. Embora exista suspeita de que a auto-imunidade possa desempenhar um papel, os auto-anticorpos não são detectados em muitos pacientes e não existe nenhum perfil específico[12-14].

Pelo fato da síndrome SAPHO poder apresentar com frequência envolvimento do esqueleto axial e mais raramente do apendicular, muitos autores têm tentado demonstrar uma relação entre esta

entidade e as espondilartrites. Contudo, a síndrome SAPHO apresenta características cutâneas, articulares e radiográficas distintas[2,8], além de um perfil de resposta imune e adaptativa diferente, com poucos auto-anticorpos detectados e níveis de produção de citocinas diferentes[12,13].

O diagnóstico diferencial da síndrome SAPHO inclui osteomielite, osteonecrose asséptica, neoplasias ósseas primárias ou metastáticas, sarcoma de Ewing, artrite infecciosa e doença de Paget[11,15]. Estudos relatam a dificuldade de se fazer este diagnóstico diferencial[11,16,17], podendo ser necessários diversos métodos invasivos e não-invasivos para a sua definição, como a cintigrafia óssea, biopsia óssea e tomografia por emissão de positrões.

Devido ao caráter crónico das lesões, que podem levar a deformidades osteo-musculares e cutâneas significativas e levam os pacientes a diversos especialistas (reumatologistas, dermatologistas, ortopedistas ou mesmo um clínico geral), alertamos para a existência da síndrome e para a necessidade do diagnóstico diferencial e tratamento adequado.

O metotrexato já tem o seu papel bem estabelecido no controle das lesões de pele de portadores de psoríase, além das manifestações articulares periféricas de portadores de espondiloartrites e de artrite reumatóide. Salientamos com este caso, uma excelente resposta com o seu uso; o controle das lesões de pele e articulares só foi obtido após a sua introdução.

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LIPOMA ARBORESCENTE SINOVIAL

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Resumo

O lipoma arborescente sinovial é uma patologia intra-articular rara e benigna, de etiologia desconhecida, caracterizada por proliferação vilosa lipomatosa do tecido sinovial. Apresenta um quadro clínico inespecífico, comumente acometendo o joelho, representado por derrames recorrentes e aumento de volume articular indolor. A ressonância magnética é o exame complementar de diagnóstico mais específico podendo muitas vezes até mesmo evitar a biópsia sinovial. Relatamos o caso de uma paciente feminina, com dor mecânica em joelhos com evolução indolente por 18 anos, compatível clínica e radiologicamente com osteoartrose. Com a constatação de aumento localizado de bursa suprapatelar unilateral sem derrame articular perceptível e aspecto ultrassonográfico de sinovite exuberante nodular, a possibilidade de sinovite vilonodular pigmentada teve de ser descartada por biópsia sinovial. Mesmo após este procedimento seu diagnóstico não foi esclarecido, sendo encaminhada à avaliação reumatológica devido a achados histopatológicos confundidos com os de artrite reumatóide. O conjunto de informações clínicas, laboratoriais, de ressonância magnética e revisão histopatológica do tecido sinovial confirmou o diagnóstico de lipoma arborescente sinovial, afastando-se a possibilidade de artrite reumatóide.

Palavras-chave: Lipoma arborescente sinovial; Sinovite vilonodular pigmentada; Artrite reumatóide.

Abstract

Synovial lipoma arborescens is a rare and benign intra-articular pathology, of unknown etiology, characterized by a villous and lipomatous proliferation of synovial tissue. It presents with atypical clinical manifestations, usually located in the knee, represented as recurrent joint effusions and painless swelling joint. The magnetic resonance is the most specific test and can often even avoid the synovial biopsy. We related the case of a female patient with mechanical pain in the knee with indolent evolution for 18 years, clinical and radiological compatible with osteoarthritis. With the finding of a localized unilateral increase of the suprapatellar bursa without perceptible joint effusion and ultrasonographic aspect of an exuberant nodular synovitis, the possibility of villonodular pigmented synovitis had to be discarded by synovial biopsy. Even after this procedure, her diagnosis was not clear, being reported to rheumatology evaluation due to histopathology findings confused with rheumatoid arthritis. The set of clinical, laboratory, magnetic resonance and histological review of synovial tissue confirmed the diagnosis of synovial lipoma arborescens, excluding the possibility of rheumatoid arthritis.

Keywords: Synovial Lipoma Arborescens; Villonodular Pigmented Synovitis; Rheumatoid arthritis.

Introdução

O lipoma arborescente sinovial (LAS) é uma patologia intra-articular rara e benigna, de causa desconhecida, não tumoral e sem envolvimento sistémico, caracterizada pela proliferação sinovial, com aspecto macroscópico de vilos arboriformes, oriunda de uma substituição difusa do tecido subsinovial por tecido abundante constituído por adipócitos maduros[1-4]. O termo proliferação vilosa lipomatosa sinovial foi sugerido em 1988 por Hallel et al[1], sendo mais adequado por ser mais descritivo e se correlacionar mais verdadeiramente com a natureza patológica não-tumoral. Os achados clínicos mais frequentes são o aumento indolor do vo-

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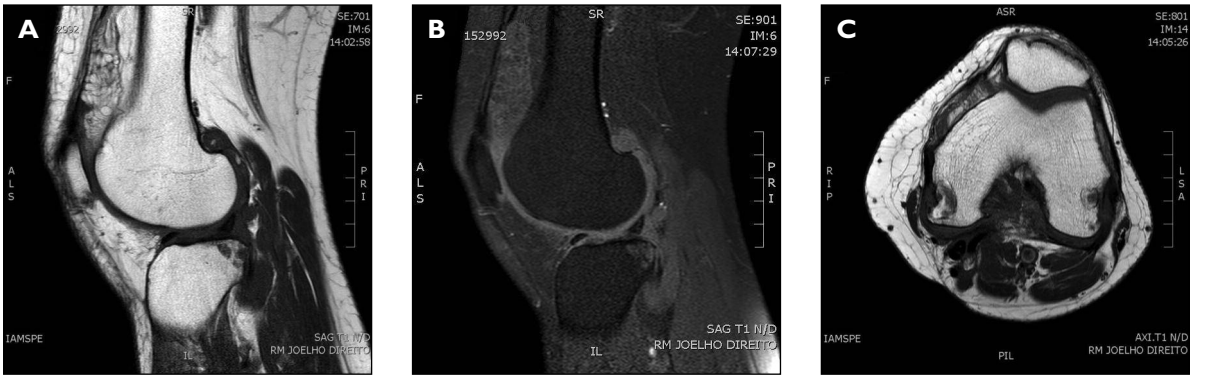

Figura 1. Ressonância Magnética de joelho esquerdo (**a**) Sagital T1: demonstra imagem sinovial de aspecto vegetante com intensidade de sinal semelhante à gordura, localizado predominantemente em recesso suprapatelar e pequenos focos infrapatelar, além de quistos subcondrais na região posterior de plateau tibial (**b**) Sagital T1 com supressão de gordura: mostra queda do sinal da lesão (**c**) Axial T1: nota-se a presença da lesão sinovial anteriormente descrita, além de duas imagens quísticas nos côndilos femurais com sinal de gordura no seu interior e pequenos osteófitos marginais.

lume articular por proliferação sinovial e derrame articular[1-3], sendo o joelho, mais precisamente a bursa suprapatelar, o local acometido com maior freqüência[1,2,4].

O conhecimento sobre o LAS por parte do reumatologista é relevante no contexto do diagnóstico diferencial de dor articular associada a derrames recorrentes e nos casos de aumento de volume articular por proliferação sinovial.

Caso clínico

Mulher de 66 anos apresentava há 18 anos quadro de dor nos joelhos de ritmo mecânico, principalmente à esquerda, intermitente, de leve intensidade, com pouco impacto na sua qualidade de vida**.** Ocorriam exacerbações esporádicas, com bloqueio e aumento de volume do joelho esquerdo, obtendo boa resposta com anti-inflamatórios não esteróides.

Evoluiu com agravamento da dor no joelho esquerdo, com radiografia evidenciando osteófitos marginais no plateau tibial bilateral e grande quisto no côndilo femural medial à esquerda, e ultrasonografia (US) mostrando alterações relacionadas com artropatia crónica associada à sinovite exuberante de aspecto nodular, aventando-se a hipótese de sinovite vilonodular pigmentada (SVNP). Foi submetida a artrotomia, a qual revelou uma lesão sinovial com múltiplas e volumosas vilosidades. A análise histopatológica evidenciou sinovite crónica vilosa sem atipias celulares compatível com artrite reumatóide, sendo encaminhada ao departamento de reumatologia para avaliação.

Apresentava aumento localizado de bursa suprapatelar esquerda, com finas crepitações bilaterais e abaulamento em fossa poplítea, sem derrame articular perceptível ou calor, com boa amplitude de movimento. Tinha provas inflamatórias normais e fator reumatóide negativo. A pesquisa do anticorpo anti-peptido citrulinado cíclico (anti--CCP) foi negativa.

A ressonância magnética (RM) com gadolíneo mostrou espessamento sinovial volumoso com sinal magnético de gordura, de aspecto frondoso, envolvendo predominantemente a bursa suprapatelar, aparência característica de LAS, além de sinais de osteoartrose associada (Figura 1). A reavaliação histológica do material da biópsia sinovial anterior mostrou intensa substituição do tecido subssinovial por adipócitos maduros e leve infiltrado linfomononuclear esparso, corroborando o diagnóstico (Figura 2).

Discussão

O LAS foi descrito inicialmente por Hoffa[5] em 1904, que o distinguiu da hiperplasia da almofada adiposa infrapatelar, denominada Doença de Hoffa, sendo o primeiro caso de LAS publicado em 1957 por Arzimanoglu[6].

O LAS atinge com maior freqüência o sexo masculino, sobretudo na idade adulta entre a quinta e sexta décadas[1-4], embora haja alguns casos relata-

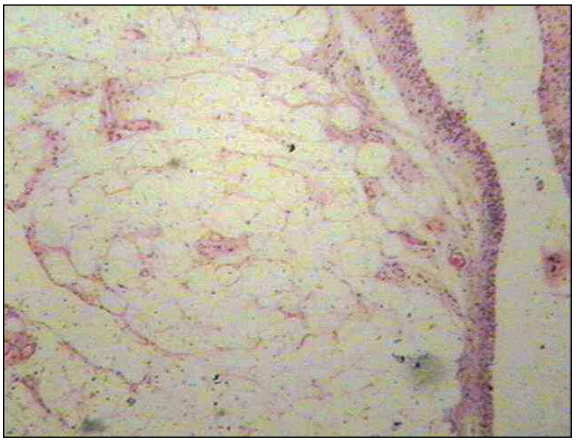

Figura 2. Histopatologia em pequeno aumento (25x) de tecido sinovial de joelho esquerdo com região subsinovial preenchida por tecido adiposo maduro, observando-se discreto/moderado infiltrado inflamatório.

dos em crianças[3,7,8]. Geralmente apresenta-se como um processo monoarticular, sendo o joelho a articulação mais afetada, particularmente a bursa suprapatelar[1,2,4], embora as ancas, tornozelos, ombros, cotovelos e punhos já tenham sido referidos como locais acometidos[1-4]. Há também casos esporádicos de envolvimento simétrico de joelhos ou ancas e mesmo casos de acometimento poliarticular[2-4].

A apresentação clínica é uniforme nos diversos relatos. A patologia pode ser oligossintomática por muitos anos, como aconteceu com nossa paciente, com o aumento do volume sinovial indolor e insidioso sendo tardiamente percebido. Sintomas mecânicos como limitação de mobilidade, bloqueio e ressalto ou períodos de exacerbação dolorosa podem ser notados na evolução e foram relacionados à insinuação de vilosidades hipertrofiadas entre as superfícies articulares[1,2,4]. Provavelmente tais sintomas devem ser mais nítidos quando associados com alterações da osteoartrose. A participação mecânica da proliferação sinovial pode ser inferida na sintomatologia de nossa paciente e mesmo visualizada em imagem com a presença das típicas vilosidades do LAS na formação dos grandes quistos subcondrais (Figura 1c). A presença de derrame articular recorrente[1-4] pode ser secundária ao grande aumento de superfície da membrana sinovial ou devido à presença de alterações relacionadas com a osteoartrose.

O aspecto anatomopatológico macroscópico do LAS consiste numa massa de aspecto arboriforme de cor branco-amarelada, devido à proliferação vilosa lipomatosa da membrana sinovial. O estudo histopatológico evidencia o acumulo de adipócitos maduros que substituem totalmente o tecido conjuntivo subsinovial, com formação de proliferações vilosas sobre a superfície sinovial. Pode haver infiltração moderada de células inflamatórias mononucleares na membrana sinovial e infiltrado focal perivascular[1-3,11].

A fisiopatologia do LAS é desconhecida. A maioria dos casos relatados não apresenta associação com outras doenças que envolvam a sinóvia primariamente. Apesar disso, a informação da relação com artropatias inflamatórias como a artrite reumatóide e artrite psoriásica, além da diabetes melitus, trauma e osteoartrose têm sido amplamente citadas[1-4]. Por outro lado, defeitos congénitos em elementos condrais, como condromalácia do plateau tibial lateral numa criança de nove anos[7] e ausência congénita de menisco medial[8], foram encontrados em associação ao LAS.

Em relação a doenças articulares inflamatórias alguns autores discutem a relação causa-efeito entre a artrite e o LAS. Enquanto Martin et al[9] sugere que o LAS ocorra como um processo reativo decorrente da estimulação nas sinovites crónicas, Ragab et al[10] postula que a sinovite inflamatória ocorre devido à presença do LAS. A osteoartrose secundária à presença do LAS parece ter uma relação mais clara, inclusive com casos relatados da sua ocorrência precoce em joelhos com LAS[11].

Testes laboratoriais como o hemograma, parâmetros inflamatórias, uricemia, fator reumatóide não demonstram alterações[1-4]. O estudo do líquido sinovial tem aspecto límpido, coloração amarela-citrino e viscosidade normal, sem aumento da celularidade ou outras alterações. Há alguns casos descritos de hemartrose, o que pode ser explicado por trauma das vilosidades sinoviais entre as superfícies articulares[2].

O exame radiológico com radiografia convencional é inespecífico, sendo possível a ocorrência de aumento de partes moles, áreas radiolucentes, além de achados mais exuberantes, como alterações quísticas e sinais de osteoartrose, nos casos de evolução mais prolongada[1,4,11]. A US pode visibilizar proliferação sinovial exuberante com aspecto viloso hiperecogénico, sem fluxo ao doppler-colorido e power-doppler, além de derrame articular[1,4,11]. A RM é o exame mais específico, tendo como achado patognomónico a presença de massa sinovial de aspecto arboriforme, com intensi-

dade de sinal semelhante à gordura em todas as sequências, artefato de desvio químico potencial na interface gordura-líquido e ausência de artefatos de hemossiderina, não ocorrendo realce após o gadolíneo[4,11]. Ryu et al[4] reviram retrospectivamente os achados de RM de oito casos de LAS, demonstrando proliferação lipomatosa de morfologia vilosa (100%), deposição subsinovial de gordura de morfologia semelhante à massa (38%), derrame sinovial (100%), erosões ósseas marginais (38%), quistos sinoviais (25%) e alterações osteodegenerativas (13%). Soller et al[12] estudando retrospectivamente treze casos de LAS do joelho identificaram três variantes no aspecto morfológico da lesão: (i) múltiplas proliferações vilosas lipomatosas da sinóvial, (ii) massa adiposa isolada subsinovial com aspecto frondoso e (iii) padrão misto.

O achado artroscópico é muito típico, visualizando-se numerosas proliferações vilosas e glóbulos com aparência gordurosa na membrana sinovial[4].

O diagnóstico diferencial deve ser feito principalmente com condições que cursam com derrame articular indolor e patologias com proliferação sinovial sem envolvimento sistémico. As massas intra-articulares, tais como a sinovite vilonodular pigmentada (SVNP), o hemangioma sinovial, a osteocondromatose sinovial e o lipoma sinovial, são as que geram maior confusão diagnóstica, sendo a RM o melhor método para diferenciar essas patologias.

No presente relato, a avaliação inicial foi de SVNP, sendo a forma localizada de SVNP o principal diagnóstico diferencial, já que essa patologia além de se caracterizar pela proliferação sinovial apresenta nódulos pedunculados localizados que podem sofrer torção e desencadear dor aguda na evolução, mimetizando parte da evolução clínica do nosso caso. Os achados de dor de leve intensidade, ausência de aumento de temperatura na articulação, ausência de derrame articular clinicamente perceptível e principalmente a ausência de grave destruição articular com doença não tratada e de longo período de evolução sintomatológica (18 anos) são argumentos contra a presença da SVNP. A ausência do recurso de RM pode ter sido o motivo da realização precoce da biópsia aberta após ultra-sonografia, cujo laudo de proliferação sinovial de aspecto grosseiro e nodular poderia ser compatível com SVNP. A imagem de RM sem o clássico artefato de hemossiderina na massa sinovial em T1 e T2 (hipossinal em ambas) e a ausência de achados histológicos de hiperplasia sinovial, macrófagos espumosos, células gigantes multinucleadas e depósito de hemossiderina em macrófagos, fibroblastos e meio extracelular, excluem definitivamente a possibilidade de SVNP.

A impressão histopatológica inicial de sinovite reumatóide levou a considerarmos a possibilidade de uma monoartrite reumatóide com instalação insidiosa e evolução policíclica com sintomas intermitentes. Porém, em nenhum momento da evolução a paciente apresentou artralgia com ritmo inflamatório, bem como sinal físico ou laboratorial de inflamação, não houve sintomas sistémicos, a pesquisa do fator reumatóide e do anticorpo anti-peptido citrulinado cíclico (anti-CCP) foram negativas e o estudo radiológico convencional não foi compatível com artrite inflamatória crónica e erosiva. A presença de infiltrado inflamatório linfomononoclear de leve a moderado no tecido sinovial é possível nos casos de LAS[1-3,11].

Quanto à possibilidade de associação etiopatogénica entre o LAS e artrite reumatóide, em nossa opinião não há nenhum racional fisiopatológico. É necessário salientar que à histopatologia o LAS demonstra mais verdadeiramente uma completa substituição do tecido conjuntivo subsinovial por tecido adiposo maduro e bem diferenciado, com volume suficiente para proporcionar grande aumento de superfície da sinóvia produzindo o aspecto arboriforme. Não se trata apenas de leve hiperplasia dos adipócitos que fisiologicamente se situam no tecido conjuntivo subsinovial ou mesmo sinoviócitos «gordurosos». O relato de alguns trabalhos da associação com artrite reumatóide é frequentemente referenciada ao relato de Weston *et al*[13] que, ao ser analisado com cuidado, pode-se inferir de que se trata de um lipoma verdadeiro intra-articular e não de LAS. Bennani et al[14], no entanto, reconhece um lipoma intra-articular em um joelho de paciente reumatóide diferenciando-o do LAS. Devemos considerar ainda a possibilidade de pacientes com LAS poliarticular em médias e grandes articulações mimetizar a artrite reumatóide em alguns aspectos, como relatado recentemente por Santiago et al[15], ou por último, a coexistência ser apenas incidental.

Embora não existam recomendações, a sinovectomia é tida como curativa pela maioria dos autores, tendo a abordagem artroscópica como opção[1-4,11]. Existem pouquíssimos casos relatados de recidiva após sinovectomia aberta. Outra modalidade possível é a sinoviortese radioisotópica,

sendo que Nisolle et al[3] relataram sucesso com o emprego do ácido ósmico em LAS do joelho. O prognóstico depende da duração da doença e das suas consequências osteoarticulares[1].

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PENILE AND SCROTUM SWELLING IN JUVENILE DERMATOMYOSITIS

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Abstract

Edema is a well-known feature of juvenile dermatomyositis (JDM). However, to our knowledge localized penile and scrotum swelling was not previously reported. During a 27-year period, 5,506 patients were followed up at the Pediatric Rheumatology Unit of our University Hospital and 157 patients (2.9%) had JDM. One of them (0.6%) had concomitant localized penile and scrotum swelling. He had severe disease activity since he was 7-year-old, manifested by diffuse cutaneous vasculitis, recurrent localized edema (limbs or face) and only one episode of generalized edema. At the age of 10, he presented edema of the genitalia associated with mild skin erythema. Penis, scrotum and testicular ultrasound as well as magnetic resonance imaging showed skin edema without testicular involvement. He was taking prednisone, methotrexate, cyclosporin, hydroxychloroquine and thalidomide. Improvement of skin rash, penile and scrotum swelling was noticed only with rituximab therapy. No adverse event was observed during anti-CD20 infusions and after six months of follow up. Penile and scrotum edema was a rare manifestation of JDM which improved with anti-CD20 monoclonal antibody treatment.

Keywords: Juvenile Dermatomyositis; Rituximab; Penis; Scrotum; Edema.

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Introduction

Juvenile dermatomyositis (JDM) is a systemic disease characterized by nonsuppurative inflammation of the skeletal muscle and skin[1,2]. The disease is initially marked by the presence of vasculitis and later on by the development of calcinosis[3].

Constitutional symptoms, such as fever, alopecia, weight loss, fatigue, headache and irritability, are usually present at the disease onset[4]. Of note, edema is a well-known feature of the disease, mainly in localized areas. The most common regions of this manifestation are eyelids, face and distal extremities[5]. Generalized edema associated with JDM was rarely reported[5-9]. To our knowledge isolated penile and scrotum swelling in JDM patients were not reported.

During a 27-year period (January 1983 to December 2010), 5,506 patients were followed up at the Pediatric Rheumatology Unit of Instituto da Criança, Faculdade de Medicina da Universidade de São Paulo and 157 patients (2.9%) had JDM. We report a unique case of a pre-pubertal JDM patient (0.6%) who presented concomitant penile and scrotum swelling without testicular involvement.

Case Report

A 7-year-old boy was diagnosed with JDM according to Bohan and Peter criteria due to Gottron s papules, heliotrope rash, muscle weakness, elevated muscle enzymes serum levels, inflammatory infiltrate and perifascicular atrophy at muscle histopathology and characteristic electromyographic changes[10]. He had severe disease activity, manifested by diffuse cutaneous vasculitis and recurrent localized edema (limbs or face) and one episode of generalized edema. He developed calcinosis in numerous sites of the body and considerable joint contractures, including elbows, wrists,

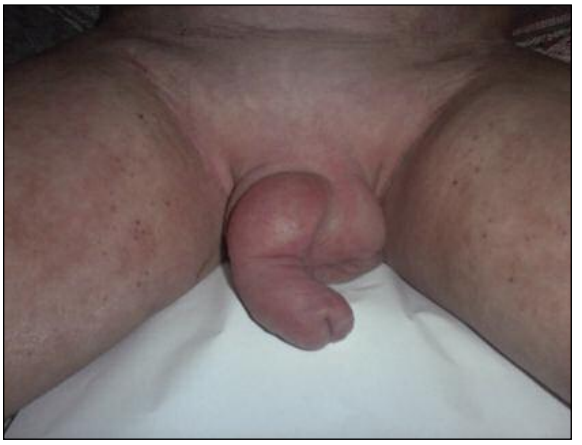

Figure 1. Penile and scrotum swellings in one juvenile dermatomyositis patient

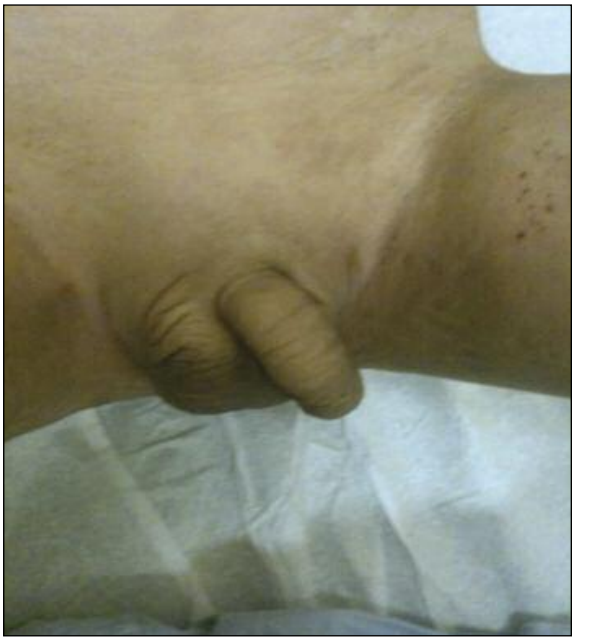

Figure 2. Improvements penile and scrotum swellings after rituximab therapy in one juvenile dermatomyositis patient

hips, knees and ankles, despite having been treated with intravenous methylprednisolone, prednisone, methotrexate, cyclosporine, hydroxychloroquine sulphate, alendronate, diltiazem, thalidomide and intravenous immunoglobulin. At the age of 10, he presented an one-month marked painless swelling of the penis and scrotum, associated with mild skin erythema in the pubic region (Figure 1). He also presented periorbital rash, erythematous maculopapular lesions on the extensor surfaces of the hands, vasculitis, photosensitivity, disseminated calcinosis, symmetric proximal weakness with a grade-3 muscle strength and significant muscle atrophy. The Childhood Myositis Assessment Scale (CMAS)[11] and the Disease Activity Score (DAS)[12] were not performed due to fixed contractures of the knees. He was taking prednisone 0.12mg/kg/day, methotrexate 1.0mg/kg/ /week, cyclosporin 5.0mg/kg/day, hydroxychloroquine 6.2mg/kg/day, alendronate 70mg/week, diltiazen 5.6mg/kg/day and thalidomide 2.3mg/kg/ /day. Erythrocyte sedimentation rate (ESR) was 62 mm/h (normal range 0-20 mm/h), aspartate aminotransferase (AST) 40 U/l (normal range 10--34 U/l), alanine aminotransferase (ALT) 32 U/l (normal range 10-44 U/l), creatine kinase (CK) 50 U/l (normal range 24-204 U/l), lactic dehydrogenase (LDH) 272 U/l (normal range 211-423 U/l), aldolase 11.8 U/l (normal range 1-7.5 U/l), albumin 4.3 g/dl (normal range 3.8-5.6 g/dl), urea 13 mg/dl (normal range 15-45 mg/dl) and creatinine 0.16 mg/dl (normal range 0.6-0.9 mg/dl). He was on pre-pubertal stage and the hormone profile was normal: follicle-stimulating hormone – FSH 4.39 IU/l (normal range 1,5-12,4 IU/l), luteinizing hormone – LH 1.09 IU/l (normal range 0,1-7,8 IU/l), and morning total testosterone 0.03 ng/dl (normal range 0,03-0,68 ng/dl). Immunological tests were positive for antinuclear antibodies (ANA) 1:640 (fine speckled pattern) and anti-Ro 52 Kd, and negative for other antibodies: anti-Mi-2, anti-synthetase (anti-Jo-1, anti-PL-7 and anti-PL-12), anti--Ku, anti-PM-Scl, anti-double stranded DNA (anti--dsDNA), anti-Sm, anti-RNP, anti-La and anti-Scl--70. Penis, scrotum and testicular ultrasound showed skin edema without testicular involvement, as it was also observed in the magnetic resonance imaging. He was treated with rituximab 375 mg/m^2/infusion for 4 weeks. After the third dose, improvement of cutaneous vasculitis and complete resolution of genital edema was already observed (Figure 2). Six months later, he had grade-4 muscle strength, maintained calcinosis, and CMAS[11] and DAS[12] could not still be performed due to the fixed contractures of the knees. Laboratory findings were ESR 26 mm/h, AST 28 U/l, ALT 31 U/l, CK 45 U/l, LDH 201 U/l and aldolase 7,5 U/l. Prednisone was suspended with maintenance of other drugs. No adverse event was observed during anti-CD20 monoclonal antibody infusions and after six months of follow up.

Discussion

To the best of our knowledge, this is the first case of genital edema without orchitis in JDM. Moreover, this manifestation was a rare finding in our Pediatric Unit.

Edema is a clinical feature of JDM, usually confined to the face or limbs. Anasarca has been rarely described at the onset and during the disease course[5-9], as reported above. Our recent Brazilian multicenter study, which included 189 JDM patients, reported facial edema in 34% at the onset of the disease and body edema in 15%[4].

The pathogenesis of edema in JDM is unknown[1,2]. This manifestation is thought to be mediated by active focal destruction of capillaries. In fact, the activation of the complement cascade induces vessel injury and capillary damage due to membrane attack complex[13]. Up-regulation of adhesion molecule expression also occurs when activated complement C5a binds to endothelial cells[1]. The widespread endothelial damage and increased capillary permeability in muscle and subcutaneous tissue may lead to hypoproteinemia and edema[14].

Our patient had an erythematous and homogeneous scrotum and penis edema. Skin infections, renal dysfunction, hypoalbuminemia and cancer were excluded, suggesting that penile edema is one possible feature of JDM. A penis carcinoma with tender swelling of the distal shaft was evidenced in one adult with dermatomyositis[15]. In fact, JDM and cancer association was observed in 2/189 (1%) patients in our Brazilian multicenter study, but no penile malignancy was observed[4].

In addition, other urogenital involvement and gonadal dysfunction associated with JDM were infrequently reported. Dystrophic calcification in ureter area was observed in one of our JDM patients[16]. Jalleh *et al* evidenced testicular necrotizing vasculitis in a 7-year-old boy suffering from this disease[17], and scrotum and testicular edema with calcinosis were also recently described in two of our JDM patients[18]. Furthermore, Moraes *et al* found minor sperm abnormalities in 5 JDM post-pubertal patients[19].

Our JDM patient had a severe disease and was previously treated with various immunosuppressive drugs concomitantly. Interestingly, genital edema improved only with rituximab therapy. This biological agent targets the CD20 molecule, leading to transient but almost complete depletion of B cells. In fact, B cells and autoantibodies participate in the etiopathogenesis of this inflammatory myopathy. This drug was beneficial in adult and pediatric patients, without severe side effects, as observed here[20,21]. Furthermore, the CD19 lymphocyte count was reduced in three JDM patients after the fourth dose of rituximab[20].

In conclusion, we report what we believe to be a rare manifestation of JDM, that is, penile and scrotum edema, which improved with anti-CD20 monoclonal antibody infusions.

Acknowledgement

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EXTENSIVE CALCINOSIS IN JUVENILE DERMATOMYOSITIS

Ernesto Cairoli*, Verónica Garra*, María José Bruzzone*, Juan Pablo Gambini**

Calcinosis is common in systemic autoimmune diseases such as juvenile dermatomyositis (JDM) or scleroderma[1]. The authors describe a 19-years-old white male with JDM diagnosed 3 years earlier because of a progressive appearance of arthralgias, proximal muscle weakness and tenderness, heliotrope rash and Gottron papules with electromyogram and muscle biopsy (deltoid) confirming the inflammatory myopathy. The patient was treated with prednisone (60 mg daily), azathioprine (150 mg daily) and hydroxychloroquine (200 mg daily), achieving clinical improvement. In the follow up, the patient presented multiple stony and tender subcutaneous nodules, localized in the extensor surfaces of both thighs, with progressive distal extension. Clinical examination revealed a large stony conglomerated mass that extended to the whole antero-external surface of the left thigh. In the right thigh, there were two isolated and non-fixed stony lumps (4 x 3 cm and 3 x 2 cm of diameter) at the external and internal surface, respectively. Serum creatinine, calcemia, urinary calcium, erythrocyte sedimentation rate, C-reactive protein, liver profile and creatine phosphokinase were within normal ranges.

Radiography and computed axial tomography scan of the lower limbs showed areas of homogeneous opacity with bony density compatible with calcium deposits in cutaneous and subcutaneous tissues, extended to the fascia in the left thigh (Figure 1). Bone scan with 99mTc demonstrated an extensive anomalous distribution of radiotracer in the soft tissues, affecting almost the entire left thigh and two circumscribed hyperintense areas in the right thigh (Figure 1). Once established the extension of calcinosis, medical treatment was started with aluminum hydroxide (30 ml 2 hours after meals), diltiazem (180 mg daily) and weekly alendronate (70 mg). After 4 months as there was no clinical improvement a low-dose warfarin (1 mg daily) was added to the treatment. After twelve months of warfarin treatment, extensive calcinosis of the left thigh decreased its surface extension, improving pain and tenderness. However, large accumulations of calcium tissue (tumoral calcinosis) showed no clinical significant changes. There were no new areas of calcinosis or local complications in pre-existing injuries.

Calcinosis cutis is a late complication of JDM, present in 20 – 70% of cases in the juvenile form[2]. It s a disorder characterized by hydroxyapatite crystals and amorphous calcium phosphates deposited in the skin and soft tissues[1,2]. In the reported case, we found ectopic calcium deposits on the skin (calcinosis cutis) and bulky subcutaneous accumulations (tumoral calcinosis) on the muscle fascia, all clinical presentations of a single pathogenic phenomenon. In the treatment of calcinosis, there is no

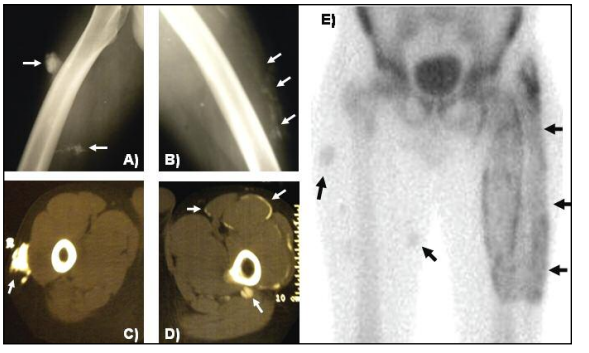

Figure 1. Identification of calcinosis in left and right thighs with different imaging methods. Lateral radiographs of the right (**A**) and left (**B**) thighs show deep and diffuse calcinosis respectively. Computed tomography of the thighs showing tumoral calcinosis in right leg (**C**) and diffuse calcifications along fascial planes of the muscles in left leg (**D**). Bone scan (**E**) shows increased soft-tissue uptake of the radiotracer with deep deposits of calcium in the right thigh and extensive subcutaneous calcinosis that spreads over almost the entire left thigh.

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evidence based on controlled studies that any of the pharmacological treatments would result in clinical benefits to establish therapeutic recommendations[1]. Different results were reported with the use of aluminium hydroxide antacids, bisphosphonates and diltiazem[1-5]. There seems to be some evidence in favour of using low-dose warfarin to treat calcinosis in systemic autoimmune diseases[5,6]. In this case, the long-term treatment with low doses of warfarin, seemed beneficial in the treatment of early and mild calcinosis but was ineffective on the injury previously established or in the large accumulations of calcinosis.

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OSTEOPOIKILOSIS IN A DIABETIC PATIENT COMPLICATED WITH ADHESIVE CAPSULITIS AND RETINOPATHY

Ali Bicer*, Koray Cogul*, Mujdat Yazici**, Ayca Sari***, Kerem Sezer****

Osteopoikilosis (OPK) is a rare osteosclerotic bone dysplasia which has an autosomal-dominant inheritance pattern and its etiology and pathogenesis remains obscure[1]. The primary problem of sclerotic bone dysplasias is impairment in bone remodeling and formation. Patients are usually asymptomatic, but 15-20% may have articular pain. Most of the reported cases have been found accidentally on radiographs taken for other purposes. Roentgenographic findings are numerous, sclerotic, well-defined circular or ovoid foci in a symmetric distribution of meta-epiphyseal areas of affected bones[2]. OPK does not require any specific treatment and it is persistent throughout life.

We herein present a case-report of a 51-year-old male patient with a poorly controlled long-term type 2 diabetes mellitus, complicated with adhesive capsulitis (AC) of the left shoulder and retinopathy in whom, OPK was diagnosed. The patient suffered from difficulty to move his left shoulder for 4 years. On musculoskeletal examination, his left shoulder active and passive ranges of motion were markedly restricted in all directions, indicating clinically an AC that was thought to be secondary to long-term diabetes mellitus.

His radiological evaluation, based on mainly anteroposterior roentgenograms revealed multiple, symmetrical, and oval-shaped periarticular sclerotic foci in varying sizes with normal joint spaces on phalanges, carpal bones and metacarpals, metatarsals and tarsal bones, distal radius and ulna, proximal humerus, clavicles, scapulae, proximal and distal femur, proximal tibia and fibula, ilia, ischia, sacrum, cervical, thoracic and lumbar vertebras, and ribs compatible with OPK (Figs 1-4). Bone scintigraphy showed no abnormality.

PK is a rare, inherited sclerosing bone dysplasia caused by the failure of resorption of secondary spongiosa, which is usually detected incidentally by plain radiographs. OPK may occur in association with several clinical abnormalities, including skin manifestations, such as dermatofibrosis lenticularis disseminate, keloid formation, hamartomas, discoid lupus erythematosus, various rheumato-

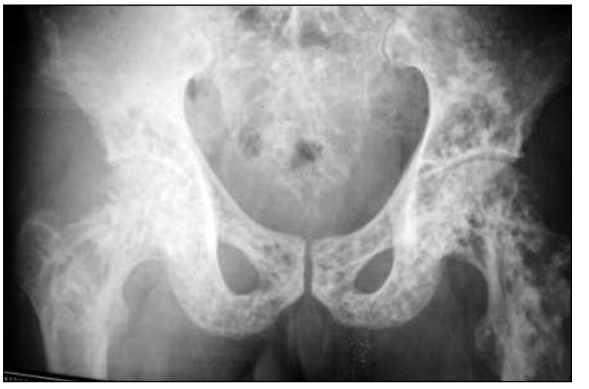

Figure 1.

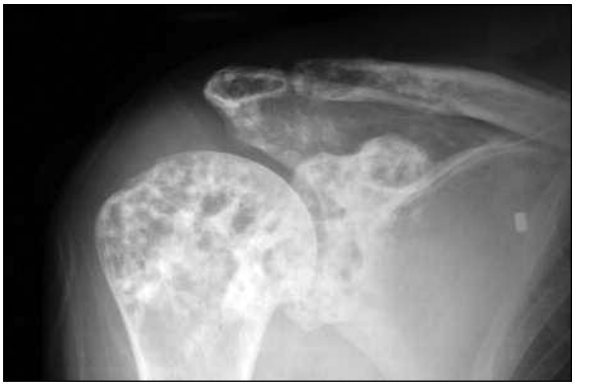

Figure 2.

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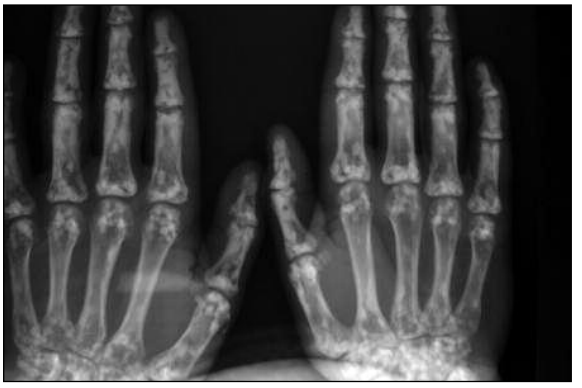

Figure 3.

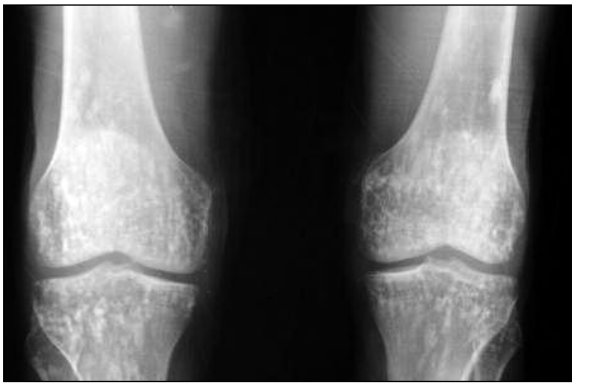

Figure 4.

logic diseases, synovial chondromatosis, and dacryocystitis[3-8]. However, OPK concomitant with an endocrine dysfunction, such as diabetes mellitus has been reported less frequently in the literature[9].

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PEDICLE SUBTRACTION OSTEOTOMY IN THE TREATMENT OF POST TRAUMATIC KYPHOSIS FOLLOWING AN OSTEOPOROTIC FRACTURE OF THE THORACOLUMBAR SPINE

Pedro Cacho Rodrigues*, Manuel Ribeiro Silva*, Nuno Neves*, Rui Pinto*

A 65-year old female patient was referred to our consultation for severe and disabling low back pain (VAS 9), with a feeling of progressive difficulty in standing straight.Two years before she had been submitted to T11 and L1 vertebroplasties for osteoporotic fractures, which provided no relief of her symptoms. On physical examination pain was elicited by pressure on the thoracolumbar junction and there was no neurologic impairment.

Radiographically, a spinal deformity was evident, with a vertebral angulation of 34º in T11 and 17º in L1, and a regional angulation of 31º and 34º, respectively. The kyphotic segment between T10 and L2 had an angulation of 51º. Respecting a pelvic incidence of 40º, we found a sacral slope of 22º and a pelvic tilt of 18º. There was no sagital imbalance.

Surgical management was achieved with a closing wedge pedicle subtraction osteotomy of T11, a L1 Smith-Petersen osteotomy and T9-L3 pedicle

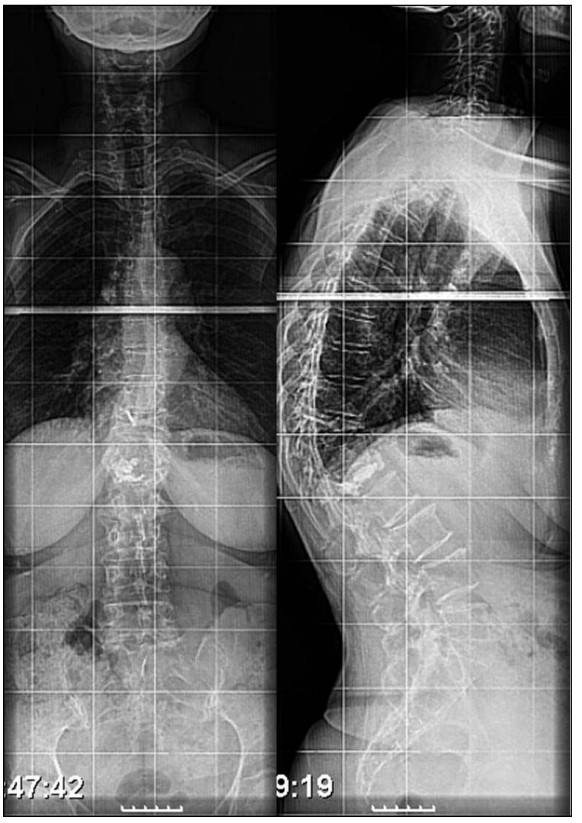

Figure 1. Pre op x-rays showing T11 and L1 fractures conditioning short segment deformity

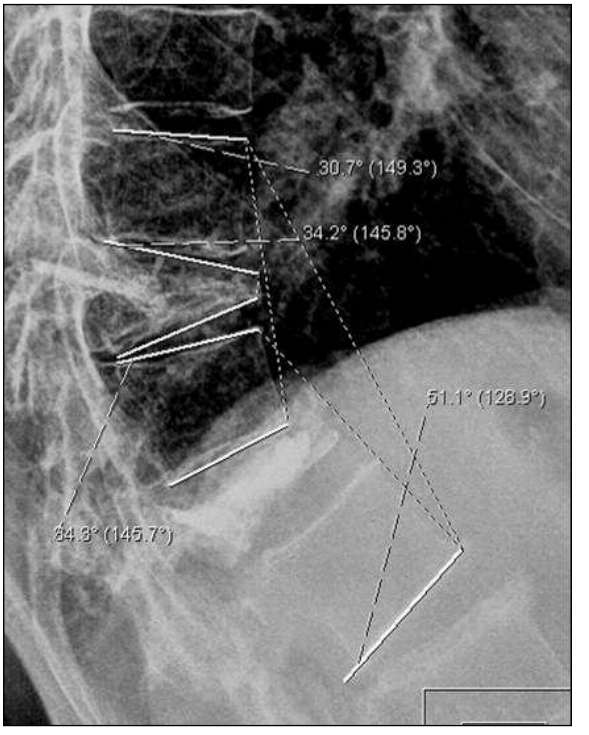

Figure 2. The kyphosis between T10 and L2 was 51°. For T11 the vertebral angulation was 34° and the regional angulation 31°; for L1 17° and 34°, respectively

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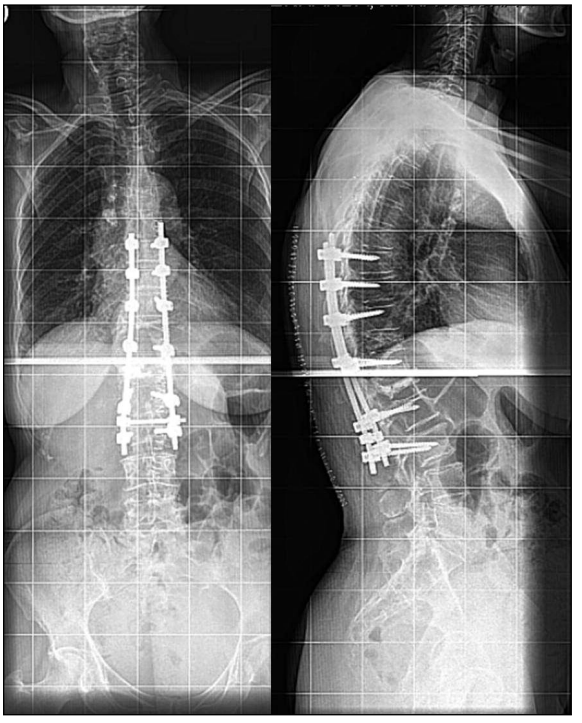

Figure 3. On post-op x-rays a good correction was obtained

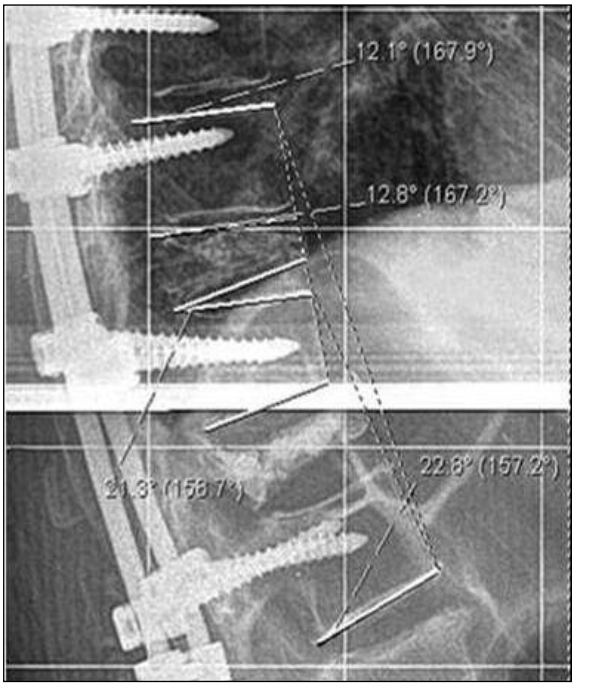

Figure 4. At 6 months follow up, the kyphosis between T10 and L2 was 23° and the vertebral angulation for T11 was corrected by 22°. The regional angulations for T11 and L1 were 12° and 21°, respectively

instrumented posterolateral fusion. There were no per or post operative complications and the patient started weight bearing at 48h post-op.

At 6 months follow up, we noticed a sound pain relief (VAS 3), and radiographically, we obtained a 22º correction of the T11 vertebral angulation, achieving 12º of T11 regional angulation, and 21º of L1 regional angulation. The global kyphosis was corrected in 28º. The pelvic parameters were corrected to 30º of sacral slope and 10º of pelvic tilt.

Vertebral fractures are extremely common in the context of osteoporosis. Nevertheless most heal uneventfully without specific treatment within a few weeks. Vertebroplasty may be indicated in selected cases but is not appropriate for unstable fractures and will not correct malalignment which can result in a symptomatic deformity, and induce severe chronic disability albeit appropriate conservative management[1,2].

The treatment represents quite a surgical challenge and should address both kyphosis correction and spine stabilization, therefore attempting to improve back pain[3]. Since the original technique described by Smith-Peterson in 1945[4] several surgical procedures have been proposed for correcting thoracolumbar kyphosis, mostly in the context of ankylosing spondylitis. However, few reports address the specific problem of local post-traumatic deformity, and the use of a closing wedge osteotomy for this purpose[5].

Although it is a technically demanding procedure, it allows excellent results in the treatment of short-angled post-traumatic kyphosis of the thoracolumbar spine[6]. The benefits of this operation are those of a single-stage surgery, with lower morbidity, lower risk of anterior pseudarthrosis, lower risks of vascular and retroperitoneal structures injury, and lower neurological risks due to forceful opening and sudden elongation of the anterior column[1]. Previous vertebroplasty does not compromise the success of this procedure.

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OSSEOUS SARCOIDOSIS

Pires-Gonçalves L*, Watt I**

A 40-year-old female presented with intermittent worsening pain, swelling, redness, and stiffness of several fingers that had been on-going for the past 5 years. Swelling, warmness, redness, and slight limitation of motion of the fourth and fifth right fingers were observed on examination. The patient was known to have sarcoidosis with involvement of the respiratory tract and *lupus pernio*, confirmed by lung biopsy 3 years previously.

Radiographs of both hands and feet demonstrated a permeative pattern of osteolysis with expansion and "tunneling" of the shafts of several phalanges in both hands and feet associated with soft tissue swelling (Figures 1 and 2). The radiographic findings described in the setting of known sarcoidosis are virtually diagnostic of osseous involvement of sarcoidosis.

Osseous sarcoidosis is rare and usually occurs with synchronous cutaneous or pulmonary disease, present in up to 80-90% of the cases[1,2]. Although patients are often asymptomatic, tenderness, pain, stiffness, and swelling of digits are not rare and can precede the radiological findings[2].

Any bone may be affected, the metacarpals and the phalanges of the hands and feet being the most commonly involved[1]. The nasal bones may also be affected particularly in the setting of *lupus pernio*[1].

Osseous lesions can manifest as lytic, permeative, or destructive lesions, which can be complicated with pathological fractures[1,2]. The distribution typically is bilateral and asymmetrical. Subcutaneous soft-tissue masses or tenosynovitis may be present also[2].

Musculoskeletal sarcoidosis can have a wide range of imaging manifestations[2,3]. Correlation with clinical and laboratorial data is essential to make the correct diagnosis. In the absence of typical extraosseous features or in rare locations such as the long bones or the axial skeleton, bone biopsy may be necessary to confirm the diagnosis[4].

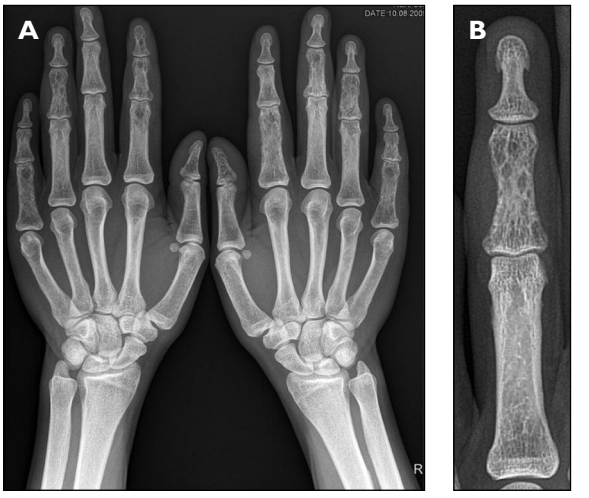

Figure 1. A. A permeative pattern of osteolysis is seen with expansion and "tunneling" of the shaft with accompanying soft tissue swelling involving the shafts of the proximal phalanges of the second and fifth digits bilaterally, the middle phalanges of the right third and both fourth digits; and the distal phalanges of the second left digit and the right thumb. Joint space width is normal. **B.** Localized view of the third finger of the left hand better demonstrates the typical lacelike lytic pattern and the tubular shape of the phalangeal shafts.

The differential diagnosis includes other granulomatous diseases including tuberculosis, histoplasmosis, coccidoidomycosis, leprosy as well as brucellosis, syphilis, Wegener's granulomatosis, hemangiomatosis, multiple myeloma, and metastasis[1].

The detection of osseous sarcoidosis may change clinical assessment of the granulomatous load, the severity of the disease, and influences treatment.

The case presented demonstrates the radiographic findings diagnostic of osseous sarcoidosis. Recognition of the typical radiographic findings of osseous sarcoidosis avoids further work-up and al-

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Case observed at the Department of Radiology of Leiden University Center, Leiden/The Netherlands

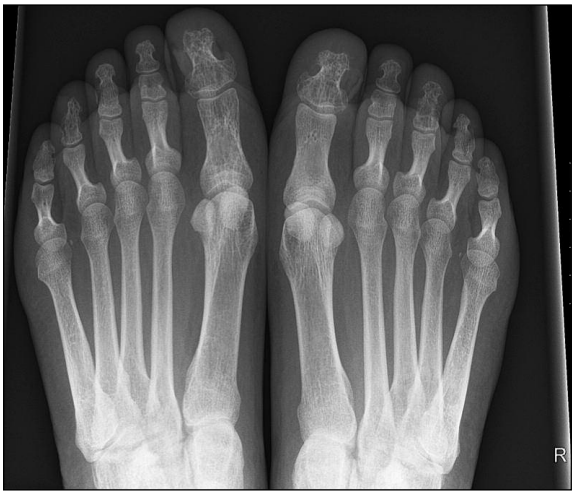

Figure 2. The distal phalanges of the right third and left fourth toes present similar trabecular architecture and bony remodeling changes. On the distal phalanges of both halluces minute cortical defects are demonstrated. The joint space width is normal.

lows clarification of symptoms, accurate assessment of disease's severity, and appropriate patient management.

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BIOLOGIC THERAPY IN PSORIATIC ARTHRITIS MUTILANS

Daniela Peixoto*, Filipa Teixeira*, Mónica Bogas**, José Costa**, Domingos Araújo***

Dear sir,

Arthritis *mutilans* is a rare but aggressive form of psoriatic arthritis that particularly affects the small joints of the hands and feet. It is characterized by osteolysis of phalanges and exuberant joint destruction, usually with preservation of neurovascular structures and tendons[1].

The use of traditional DMARDs in this clinical situation has been disappointing. The description of the use of biotechnological agents in mutilating arthropathy is still very scarce, with only two publications found in the literature[2,3].

The authors wish to share their experience with the use of an anti-TNF agent in arthritis *mutilans*. We describe a case of a male patient, aged 39-year-old when first seen in our Rheumatology department. He had had the diagnosis of psoriatic arthritis for about 20 years. Despite the NSAID and conventional DMARD treatment with methotrexate, he developed a significant deforming destructive arthropathy of the hands, typical of a mutilating form, with telescoping of the right 4th and 5th fingers and the left 4th finger[4]. Laboratory findings revealed persistently high biological parameters of inflammation (mean ESR around 41mm and mean PCR 2.19 mg/dL).

The patient started treatment with etanercept at a dose 50 mg/week in combination with methotrexate and has been treated yet for two years, with normalization of the acute phase reactants, improvement of functional capacity with an mean initial HAQ of 1.5 and last HAQ of 0 and no progression of radiographic lesions (Figures 1 and 2).

Despite the absence of scientific evidence regarding the treatment of *mutilans* arthropathy with anti-TNF therapies, experience with these drugs in other clinical forms of psoriatic arthritis and the progressive destructive evolution with consequent functional impairment in a young patient led us to consider this treatment in this case, with apparent stabilization and no adverse effects to report, so far.

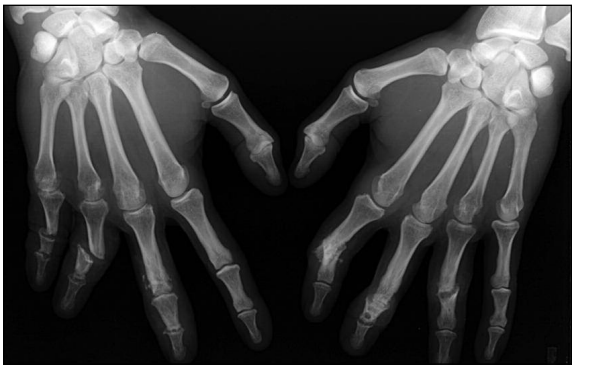

Figure 1. Hand radiography (2008) – Articular destruction of several interphalangeal joints

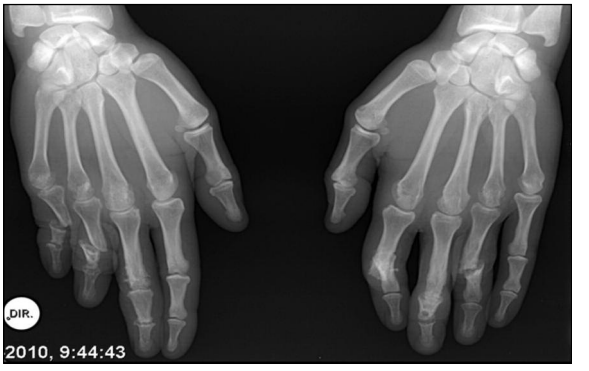

Figure 2. Hand radiography (2010) – Stabilization of radiological lesions

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Page 1

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Page 2

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Name(s) and initials of author(s) of chapter. Chapter title. In: Name(s) and initials of editor(s). Book title. City: Name of publisher, year of publication: pages.

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