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Drug-Induced Musculoskeletal Disorders

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Abstract

Drug-induced musculoskeletal disorders represent a broad clinical spectrum, from asymptomatic biological abnormalities to severe and even life-threatening diseases. Since an increasing number of drugs have been implicated in inducing rheumatic symptoms and/or syndromes, this review is not meant to be exhaustive, bearing in mind that the development of any musculoskeletal disorder should be considered as possibly related to a medication.

The purpose of this article is to provide an overview of the more frequent drug-induced musculoskeletal disorders. These include: (i) arthralgias and arthropathies, including chondropathies and inflammatory arthritis; (ii) connective tissue diseases, especially lupus-like syndromes; (iii) periarticular disorders, including tendinopathies, enthesopathies and frozen shoulder; (iii) bone diseases, such as osteoporosis, osteomalacia and osteonecrosis; and (iv) myopathies. Although virtually all drug classes may induce musculoskeletal disorders, a significant part of them are related to corticosteroids, vaccines, antibacterials and lipid-lowering agents.

Knowledge of drug-induced musculoskeletal disorders avoids carrying out unnecessary investigations, and allows optimal management of the patients, i.e. early discontinuation of the offending agent, adequate treatment monitoring and/or intervention with appropriate preventive actions.

Drug-induced musculoskeletal disorders represent a broad clinical spectrum, from asymptomatic biological abnormalities to severe and even life-threatening diseases, although arthralgia/myalgia is the only feature in many cases. Of note is that both the clinical presentation and severity of these disorders may vary from one patient to another for the same drug, depending on the dose employed, the duration of therapy, the pathophysiological status of the patient and/or genetic and environmental factors.[1]

A vast array of drugs has been implicated in inducing rheumatological adverse events. For some compounds, there is pharmacological or epidemiological evidence for a causal link with the development of a specific rheumatic disorder, but for many, one relies upon isolated case reports.[2] In view of the escalating number of drugs that have been implicated, along with the great diversity of drug-induced musculoskeletal disorders, this review is not meant to be exhaustive.

Early recognition of these adverse effects is important because it avoids carrying out unnecessary investigations. Furthermore, symptoms often resolve on withdrawal of the offending agent. Consequently, an iatrogenic origin should be considered in any patient presenting with rheumatic symptoms or syndromes.[1-4] Moreover, physician awareness of these risks may highlight the need for treatment monitoring and allow for intervention with preventive measures.[3]

This article will focus on medically significant drug-induced musculoskeletal disorders, with the aim of helping physicians to recognise, manage and/or prevent them.

1. Arthropathies Related to Cartilage Damage (Chondropathies)

1.1 Quinolone Antibacterials

There is experimental evidence that both first generation quinolone antibacterials (e.g. nalidixic acid) and fluoroquinolones can produce cartilage lesions, particularly in weight-bearing joints in young animals.[5] In humans, there have been numerous reports of non-erosive arthropathies that frequently involved the lower extremities and often occurred in patients with cystic fibrosis.[6] However, the incidence of arthropathies associated with these fluoroquinolones may have been overestimated in these patients, since the disease itself is known to induce joint disturbances.[5]

Articular symptoms generally appear in the first 2 weeks after the drug is started, although late onset is also possible.[1] The symptoms usually consist of arthralgia with or without myalgia; incapacitating arthropathies and joint effusions are uncommon.[3] After stopping the antibacterial, symptoms generally resolve within 2 weeks to 2 months, without any radiological sequelae.[1,3,5]

Since these arthropathies preferentially occurred in young patients, fluoroquinolones have been contraindicated in children and adolescents in the growing phase as well as during pregnancy and lactation.[3] However, patients with a history of nalidixic acid therapy during childhood showed no excess risk of joint diseases in adulthood.[5] Similarly, in a retrospective study of 1795 children treated with ciprofloxacin, the incidence of arthralgia was 1.5% and reversible in all cases.[6] Furthermore, magnetic resonance imaging showed no abnormalities of the cartilage in children receiving ciprofloxacin for up to 3 months.[3,7] Accordingly, fluoroquinolones may be beneficial in treating serious paediatric infections when conventional therapy has failed or resistance has emerged.[7]

1.2 NSAIDs

Early reports incriminating NSAIDs in hastening radiographic deterioration of osteoarthritis of the hip and knee were anecdotal.[8] The favoured explanation was mechanical overuse of a joint rendered less painful by NSAID therapy.[8] Both retrospective and prospective clinical studies undertaken in the 1980s–90s generated inconsistent data and they were criticised for their methodological flaws and weaknesses.[8] Moreover, experimental studies showed that NSAIDs variably affected cartilage metabolism or influenced animal models of osteoarthritis.[3,8] Based on these data, the causal relationship between more severe joint damage and NSAID intake has been considered unproven.[3]

However, a recently published population-based prospective cohort study reopened the debate.[9] In this study, long-term use of diclofenac, unlike that of ibuprofen, naproxen and piroxicam, was associated with a >2-fold increase in radiologic progression of hip or knee osteoarthritis.[9] A potential limitation of this study is that the estimation of NSAID use was based on the prescriptions, and not the actual intake of NSAIDs.[9] Finally, the authors concluded that "there is a clear need to further investigate the influence of individual types of NSAIDs on cartilage metabolism in a clinical situation".[9]

1.3 Intra-Articular Corticosteroids

The classical view is that intra-articular corticosteroids may accelerate joint damage as a result of their catabolic effects.[10] Moreover, several cases of rapid joint destruction (Charcot-like arthropathy) have been observed, especially in patients who received repeated corticosteroid injections.[1,3] Conversely, experimental works suggest that corticosteroids might display beneficial effects by reducing proteolytic enzymes and interleukin-1β levels within joints.[10]

In a small retrospective cohort of 13 patients with rheumatoid arthritis, arthroplasty was not more common in the heavily injected joints (four or more injections per year) after an average follow-up of 7.4 years.[11] In a randomised, double-blind trial, 68 patients with knee osteoarthritis received intra-articular injections of either triamcinolone acetonide 40mg or saline every 3 months for up to 2 years.[12] Measurement of the radiographic joint space width

after 2 years of treatment revealed no differences in the anatomical progression of the disease between the two groups.[12] Thus, judicious use of intra-articular corticosteroids (four or less injections per joint and per year) appears to convey a very small risk, if any, of joint damage.[3,12] On the other hand, there is no evidence that intra-articular corticosteroids may prevent cartilage degradation in humans.[12]

2. Inflammatory Arthritis

2.1 Crystal-Induced Arthritis

2.1.1 Hyperuricaemia and Gout

Diuretics (thiazides and loop diuretics, such as furosemide and bumetamide) are the major causes of drug-induced hyperuricaemia, which results from decreased renal excretion of uric acid.[1,13] However, gout is rarely observed, even in patients receiving long-term diuretics. Interestingly, tophi may develop in the absence of acute gout flares.[1] Some advocate that patients with urate concentrations >100 mg/L should be treated with an urate-lowering drug if withdrawal of the diuretic is not possible;[3] others advise against prescribing such treatment for asymptomatic hyperuricaemia in patients with intact renal function.[14,15] It should be stressed that the frequency of acute flares may increase in patients with chronic gouty arthritis initiating treatment with urate-lowering drugs.[14-16] Since colchicine is effective in reducing the frequency and severity of gouty attacks under these circumstances, its prophylactic use is generally recommended.[15,16]

Hyperuricaemia and, to a lesser extent, gout are common complications in organ transplant recipients receiving ciclosporin or tacrolimus.[1,13,17,18] Besides these immunosuppressants, several factors, including kidney or heart transplantation, renal failure, male sex, older age, higher body mass index and diuretic use contribute to the development of post-transplant hyperuricaemia.[18,19] A retrospective survey conducted in the US showed a 3-year cumulative incidence of new onset gout of 7.6% after renal transplantation.[18] Patients receiving ciclosporin were more likely to develop gout than those receiving tacrolimus.[18] Since hyperuricaemia and gout may be independent predictors for graft loss and death, strategies to decrease uric acid levels should be considered in this population.[18,19] These include nutritional management, avoidance of diuretics, decrease or avoidance of ciclosporin treatment and use of urate-lowering agents.[19]

Ethambutol and pyrazinamide that are used in the chemotherapy of tuberculosis, can induce hyperuricaemia, and a few cases of acute gout have been ascribed to these agents.[1] Of note, pyrazinamide can also induce arthralgia unrelated to hyperuricaemia.[1] At low doses, salicylate intake is associated with a modest increase in uric acid levels.[1] The risk for acute hyperuricaemia after starting cytotoxic treatment of the myelopropoliferative disorders and other malignancies warrants preventive treatment.[1]

Other drugs might precipitate acute gout: retinoids, lipid-lowering drugs (nicotinic acid, gemfibrozil), vitamin B_1 (thiamine) and B_{12} (cyanocobalamin), histamine H_2 receptor antagonists and proton pump inhibitors.[1,3] A large cohort study did not indicate that current omeprazole use was associated with an increased risk of developing gout, either in comparison with recent use or in comparison with current use of H_2 receptor antagonists.[20] However, this does not exclude the possibility that these antiulcer agents may cause or trigger gout in particular individuals.[20]

2.1.2 Pseudogout

Pseudogout manifests as an acute arthritis with the presence of calcium pyrophosphate dihydrate crystals in synovial joint fluid. Bisphosphonates might very occasionally trigger acute attacks of pseudogout.[21]

Intra-articular injections of hyaluronic acid preparations, often termed viscosupplementation, have been advocated for symptomatic treatment of knee osteoarthritis although their effectiveness has recently been called into question.[22] These injections may produce local reactions (joint pain and/or acute synovitis), which are typically benign and short lived, and resolve in a few days without sequelae.[23,24] However, on rare occasions, post-injection

flares are severe and even mimic a joint infection.[23-25] In some cases, acute arthritis following intra-articular hyaluronic acid was related to pseudogout.[23-25] These local reactions do not necessarily recur with subsequent injections.[23] Nevertheless, their frequency was reported to increase in patients receiving more than one course of treatment.[26]

2.1.3 Intra-Articular Corticosteroids

Intra-articular corticosteroid instillations result in a localised inflammatory flare in about 1–4% of patients.[3] These flares usually begin within a few hours of the procedure. They subside within a few days with aspiration, application of ice and/or oral NSAIDs.[1,3] These reactions may be a form of corticosteroid crystal-induced synovitis.[1,3,10] Accordingly, they are probably more frequent with poorly soluble and needle-shaped corticosteroid crystals, such as triamcinolone hexacetonide.[1,3] Arthrocentesis should be performed to exclude infection.[10]

Because of its severity, septic arthritis is the most feared complication of intra-articular corticosteroid therapy.[10] Fortunately, this complication is quite rare: its frequency has been estimated to be about 1 case per 14 000–50 000 procedures.[3] It has been suggested that the more incapacitated rheumatoid patients and those receiving cytotoxic drugs were at greater risk.[10] Preventive measures include strict adherence to aseptic procedures and injections through areas of undamaged skin.[10] Furthermore, distant infections should be eradicated before joint injection is undertaken because corticosteroids may reduce the joint's defences against transient bacteraemia.[10]

2.2 Vaccines

It is well known that musculoskeletal symptoms (arthralgia, arthritis) may occur in response to different types of immunisation.[27] In this respect, there have been a number of case reports of monoarthritis or polyarthritis occurring after hepatitis B and rubella vaccinations or bacillus Calmette-Guérin (BCG) administration.[1,28] There have also been anecdotal reports of arthritis that developed after immunisation with other vaccines, including tetanus, influenza, typhoid, mumps, measles and smallpox vaccines.[1,28] In most cases, the musculoskeletal symptoms were self-limiting.[27] However, persistent polyarthritis, including definite rheumatoid arthritis have also been observed. These appeared to be no different from other forms of inflammatory polyarthritis, suggesting that immunisation may trigger inflammatory rheumatic diseases in patients with underlying immunological or genetic susceptibility.[27] This does not preclude the possibility that the relation between vaccination and arthritis may be coincidental in many cases.

2.2.1 Hepatitis B Vaccine

In many instances, adverse effects following hepatitis B vaccination mirror the extrahepatic manifestations experienced by patients with hepatitis B virus infection.[29] Unsurprisingly, nearly 1% of adult vaccine recipients may experience transient arthralgia and polyarthritis, with an initial onset of symptoms from 1 to 4 weeks after immunisation.[1] Human leukocyte antigen (HLA) B27-positive patients may develop reactive arthritis resembling Reiter's syndrome.[1]

There is still controversy about whether or not a causal relationship exists between rheumatoid arthritis and hepatitis B vaccination. Epidemiological studies undertaken in the early 1990s did not show any relationship between hepatitis B vaccine and autoimmune disorders, including rheumatoid arthritis.[30] These data have been challenged by those of recent case-control studies conducted using the US Vaccine Adverse Event Reporting System (VAERS) database.[29,31] Based on reports to VAERS from July 1990 through May 2004, it appeared that adults receiving hepatitis B vaccination had significantly increased odds ratios (ORs) for various serious autoimmune adverse events, particularly arthritis (OR 2.01; 95% CI 1.3, 3.1), rheumatoid arthritis (OR 18; 95% CI 3.1, 740), systemic lupus erythematosus (SLE) [OR 9.1; 95% CI 2.3, 7.6] and vasculitis (OR 2.6; 95% CI 1.03, 8.7) in comparison to an adult tetanus-diphtheria vaccine population who served as a control group.[29] Furthermore, some case reports describe the onset of

rheumatoid arthritis following a first vaccine injection, with recurrence or worsening of the articular symptoms after a second injection.[30] Conversely, a small cohort study showed that hepatitis B vaccination was not accompanied by an exacerbation of rheumatoid arthritis, possibly because of an inadequate sample size.[32] Finally, when HLA-DR typing was performed, most patients with postvaccinal rheumatoid arthritis were found to express HLA class II molecules (HLA-DR4 and/or HLA-DR1) associated with rheumatoid arthritis.[30,33] Thus, it may be hypothesised that the vaccine recombinant peptides could bind to class II MHC molecules and trigger T cell proliferation, initiating early events leading to rheumatoid arthritis.[33]

In summary, there is some evidence that hepatitis B vaccination may trigger rheumatoid arthritis in susceptible patients. However, this vaccine is safe in a large majority of patients, and there is no doubt that its benefits overall far outweigh its risks, especially in patients at risk for contracting hepatitis B virus infection.[31]

2.2.2 Rubella Vaccine

Like natural rubella infection itself, rubella vaccination is a cause of acute joint symptoms, particularly in women.[28] These symptoms are usually fleeting. However, it has been suggested that rubella vaccination might lead to significant chronic arthropathy.[28] Results from a randomised, double-blind, placebo-controlled trial indicated a significantly higher incidence of acute joint manifestations in vaccine recipients (30%) than in placebo recipients (20%).[34] Furthermore, there was a small excess of chronic arthralgia or arthritis in the vaccine group compared with the controls (OR 1.58; 95% CI 1.01, 2.45).[34] Similarly, an analysis of the VAERS database revealed that rubella vaccinations were associated with a statistically significant increased hazard of chronic arthritis in adults.[35] Conversely, a large retrospective cohort study found no evidence of a relationship between immunisation with rubella vaccine and persistent joint symptoms in an adult female population.[36]

Although acknowledging the fact that rubella vaccination may be a cause of persistent or recurrent joint manifestations in susceptible women, it should be stressed that wild rubella infection appeared to be associated with a higher incidence, increased severity and more prolonged duration of joint symptoms than is seen after rubella immunisation.[37] Finally, considering the risk of congenital rubella, girls and women of childbearing age should be offered rubella vaccine until circulation of rubella virus is eliminated.[38]

2.2.3 Bacillus Calmette-Guérin Therapy

Intravesical BCG instillations that are used to treat superficial bladder carcinoma are followed by arthralgia in 0.5–5% of cases.[1] Moreover, aseptic arthritis has been described in 0.4–0.8% of a large series of patients receiving this therapy.[39] In most cases, it consisted of oligoarthritis involving mainly the lower limb joints, especially the knees, and usually occurred after 4–8 weeks of BCG therapy in HLA-B27-positive patients.[39] Concomitant urinary symptoms (dysuria, haematuria) or signs of ocular inflammation (conjunctivitis, uveitis) were not uncommon. Radiological evidence of sacroiliitis was seen in about 20% of cases, and some patients presented with documented ankylosing spondylitis.[39] Finally, 90% of patients responded well to NSAIDs with a total clinical recovery within 6 months.[39] These features are very suggestive of reactive arthritis.[1,39]

Interestingly, the route of administration may influence the clinical presentation of BCG-induced arthritis.[39] Symmetrical polyarthritis resembling rheumatoid arthritis has been described in patients receiving intradermal BCG injections used to enhance antitumour immune response.[39]

2.3 Cytokines

Cytokine immunotherapy is used in an expanding list of chronic medical conditions. The spectrum of adverse effects related to a given cytokine depends on the biological properties of the molecule itself, its dosage regimen and mode of administration as well as the underlying disease.[40]

Interferon-α is prescribed in type B and C chronic viral hepatitis and various malignancies.[40,41] In addition to antiviral and antitumour activities, in-

terferon-α possesses immunomodulatory effects; hence, its use may lead to autoimmune disorders, such as thyroiditis and, more rarely, connective tissue diseases, especially SLE.[41] Moreover, interferon-α therapy may induce arthralgia and exacerbate pre-existing hepatitis C virus-related arthritis.[42,43] It may also be responsible, albeit rarely, for induction of rheumatoid-like polyarthritis.[41] In that case, joint symptoms generally disappear with NSAIDs or prednisone and/or cessation of interferon-α therapy.[41-43] Disease-modifying antirheumatic drugs (DMARDs) may prevent recurrence of polyarthritis after restarting interferon-α therapy in these patients.[42] New onset inflammatory arthritis has also been described in patients with multiple sclerosis receiving interferon-β therapy.[41,43] However, interferon-β is thought to exert a predominantly anti-inflammatory effect, and some studies have suggested that patients with rheumatoid arthritis may benefit from its use.[41]

Common clinical indications for the recombinant interleukin-2, aldesleukin include metastatic renal cell carcinoma and malignant melanoma.[41] This cytokine has been implicated in the induction of rheumatoid arthritis, psoriatic arthropathy, ankylosing spondylitis and Reiter's syndrome.[41]

Granulocyte and granulocyte-macrophage colony stimulating factors, such as filgrastim, lenograstim and molgramostim may induce bone and muscle pain during the neutrophil recovery phase.[44] These cytokines have also been reported to cause flare-up of rheumatoid arthritis, especially in patients with Felty's syndrome, and induce acute polyarthralgia and myalgia.[41,44]

2.4 Arthritis Related to Other Drugs

There have been many case reports and case series of acute arthralgia or arthritis in close time association with a number of drugs. Most commonly involved drugs or drug classes are listed in table I.[1,45-51] Of note is that, in many instances, joint symptoms were a feature of drug-induced vasculitis.[1,45]

It is well established that patients receiving high doses of bisphosphonates may experience flu-like symptoms with myalgia, arthralgia and/or bone pain, which have been ascribed to an acute-phase response.[52] Similar rheumatic symptoms, often described as 'disabling' or 'incapacitating', and acute polyarthritis have also been reported in osteoporotic patients treated with bisphosphonates.[53,54] After discontinuation of the drug treatment, some patients experienced immediate improvement whereas the majority had more gradual improvement.[54]

Transient joint pain, swelling and muscle stiffness may occur in 15–30% of patients with transfusional iron overload receiving deferiprone.[55,56] Furthermore, an underlying thalassaemic osteoar-

Table I. Principal drug and drug classes involved in the development of various types of inflammatory arthritis (excluding gout and pseudogout)

Drug classes	Undisputed causative agents	Possible causative agents
Vaccines	Hepatitis B and rubella vaccines, BCG (intravesical)	Influenza, measles, mumps, smallpox, tetanus and typhoid vaccines
Cytokines and antagonists	Interferon-α	Interferon-β, interleukin-2, G-CSF and GM-CSF, anti-TNF
Antiarythmic drugs		Quinidine
Antibacterials		Fluoroquinolones, minocycline, cefaclor
Antihypertensive agents		β-Adrenoceptor antagonists, ACE inhibitors, hydralazine
Antiulcer agents		Histamine H_2-receptor antagonists, PPIs
Drugs acting on haemostasis		Clopidogrel and ticlopidine, streptokinase
Drugs acting on bone turnover		Bisphosphonates
Psychoactive agents		Antidepressants, including bupropion

BCG = bacillus Calmette-Guérin; **G-CSF** = granulocyte-colony stimulating factor; **GM-CSF** = granulocyte-macrophage colony stimulating factor; **PPI** = proton pump inhibitor; **TNF** = tumour necrosis factor.

thropathy may be worsened as well as improved by iron-chelating therapy.[55]

3. Connective Tissue Diseases

3.1 Drug-Induced Systemic Lupus Erythematosus

Drug-induced SLE account for about 5% of all cases of SLE.[57] Accordingly, the prevalence of drug-induced SLE is estimated to be 0.5–2.5 per 100 000 population,[57] but it might be higher since many cases are mild and may be unrecognised.[58] In contrast to idiopathic SLE, males are equally as likely as females to develop drug-induced SLE.[58,59]

The latter usually resembles mild idiopathic SLE and commonly presents as arthralgia (90% of the patients), myalgia (50%) associated with fever, malaise and/or serositis (pleurisy, pericarditis).[58,59] Cutaneous manifestations, usually in the form of a maculopapular rash, are seen in up to 30% of the patients.[57] Conversely, malar rash, discoid lesions, alopecia and photosensitivity, commonly observed in idiopathic SLE, are infrequent.[58] Raynaud's phenomenon is also unusual.[57] CNS and renal involvement are usually absent.[58] In addition to high erythrocyte sedimentation rate (ESR), possible laboratory findings include mild anaemia, leucopenia or thrombocytopenia as well as positive Coomb's test.[57,58] A positive antinuclear antibodies is a universal finding and most frequently shows an homogeneous staining pattern because the autoantibodies are usually directed against nuclear histone proteins.[57-59] Although antihistone antibodies are characteristic of drug-induced SLE, they are not specific for the syndrome and are found in a virtually similar proportion of patients (75%) with idiopathic SLE.[57,58] Other antinuclear antibody specificities may be found in drug-induced SLE. Antibodies to single-stranded DNA are relatively common whereas typical markers of idiopathic SLE, namely anti-double-stranded DNA (ds-DNA) or anti-Sm antibodies, occur in <5% of patients or are absent, respectively.[57-59]

In summary, the diagnosis of drug-induced SLE may be based on the following criteria:[3,58]

- absence of features suggestive of idiopathic SLE and/or antinuclear antibodies before taking the suspected drug;
- continuous treatment with the suspected drug for at least 1 month;
- common presenting symptoms: arthralgia, myalgia, malaise, fever, serositis;
- positive antinuclear antibodies caused by antibodies to histone, in the absence of other antinuclear antibody specifities, including anti-ds-DNA and anti-extractable nuclear antigens;

Table II. Principal drugs and drug classes implicated in the development of drug-induced systemic lupus erythematosus[57-60]

Definite causal link	Probable causal link	Possible causal link
Chlorpromazine	Antiepileptic drugs	ACE inhibitors
Hydralazine	Antithyroid drugs	Calcium channel antagonists
Isoniazid	Anti-TNF	Clobazam
Methyldopa	β-Adrenoceptor antagonists	Clozapine
Minocycline	Penicillamine	Deferiprone
Procainamide	Fluorouracil agents	Estrogens and oral contraceptives
Quinidine	Hydrochlorothiazide	Gold salts
	Interleukin-2	Griseofulvin and azole antifungal agent
	Interferons	Lithium
	HMG-CoA reductase inhibitors	NSAIDs
		Penicillin
		Sulfonamides
		5-aminosalicylates (sulfasalazine)
		Zafirlukast

TNF = tumour necrosis factor.

- symptom improvement within days or few weeks, and recovery within 1 year after discontinuation of the suspected drug.

However, recognition of a drug-induced SLE may be difficult in patients with pre-existing rheumatic disorders, especially rheumatoid arthritis.[59]

The agents that can cause drug-induced SLE can be divided into three groups (table II).[58] These drugs are remarkable for their biochemical and pharmacological diversity.[57] However, drug-induced SLE may be a class effect in some cases (e.g. antithyroid drugs, anti-tumour necrosis factor [TNF] agents, β-adrenoceptor antagonists, HMG-CoA reductase inhibitors ['statins']).[57,58,60] Some medications are known to induce a positive antinuclear antibodies (e.g. isoniazid, penicillamine), and even anti-ds-DNA antibodies (e.g. anti-TNF agents) in a high proportion of patients, but only a small fraction of these patients experience clinical signs of SLE.[57,60-63] In this respect, it should be remembered that the development of a positive antinuclear antibodies in its own right is not an indication for stopping treatment.[57] The offending drug should be discontinued only if the patient becomes symptomatic or develops haematological abnormalities such as leucopenia or a rising ESR.[57]

3.2 Polymyositis and Dermatomyositis

Drug-induced polymyositis and dermatomyositis are very rare, with those caused by penicillamine being the best described.[2] Typical polymyositis and dermatomyositis have also been attributed to tiopronin, a sulfhydrylated derivative close to penicillamine, as well as to antithyroid drugs, lipid-lowering agents (fibrates, statins), cytokines (interferon-α, interleukin-2), antibacterials (penicillin, sulfonamides, minocycline), selective β_2-adrenoreceptor antagonists, gonadotropin-releasing hormone (GnRH) analogues, alfuzosin, azathioprine, cimetidine and hydroxycarbamide.[4] However, there have been only isolated case reports for the majority of these compounds.[4] In common with drug-induced SLE, withdrawal of the offending drug represents the mainstay of therapy.[4]

3.3 Scleroderma-Like Conditions

Drug-induced systemic scleroderma-like syndrome is characterised by tightening or sclerosis of the skin, especially in acral areas, Raynaud's phenomenon and myalgia associated with antinuclear antibodies and sometimes anti-Scl-70 antibodies and cessation or reversibility of the process after discontinuation of the offending agent.[59]

Apart from tryptophan, an amino acid that had been used to treat insomnia and was associated with a large outbreak of scleroderma-like disorders and eosinophilia-myalgia syndromes, there have been few reports of drug-induced systemic scleroderma.[59,64] Drugs that have been implicated in inducing this adverse effect include bleomycin, ergot alkaloids, penicillamine, appetite suppressants, especially amfetamine-related compounds, ethosuximide, cytokines and fosinopril.[64]

4. Periarticular Disorders

4.1 Tendinopathies

Drug-induced tendinopathies are mainly ascribable to fluoroquinolone antibacterials or corticosteroids.

The actual incidence of fluoroquinolone-induced tendon injury is unknown, but has been estimated to range from 0.14 to 0.4%.[65] A nested case-control study among users of fluoroquinolones in a UK general practice database indicated that the overall excess risk of Achilles tendon disorders is 3.2 cases per 1000 patient years.[66] According to a similar study, 2–6% of all Achilles tendon ruptures in people aged >60 years can be attributed to quinolones.[67] Risk factors most frequently associated with this adverse effect include age >60 years, concomitant use of corticosteroids and renal failure.[65-67] Though being a class effect, tendon disorders are likely to be more frequent with pefloxacin and ofloxacin use than with other fluoroquinolones.[67,68] The latency period between start of treatment and onset of symptoms is typically 1–2 weeks.[65] However, tendon injury may develop within hours after the initial dose to as long as

months after the initiation of treatment and even after discontinuation.[65] Fluoroquinolone-induced tendinopathies are often bilateral and exhibit a marked predilection for the Achilles tendons.[65] Pain and functional disability are the leading symptoms. Partial or complete tendon rupture has been described in almost half the reported cases of Achilles tendinitis, and may occasionally be the revealing feature.[65] It is imperative to stop the drug at the earliest signs of tendon damage.[65] The treatment mainly consists of placement of tendon at rest and administration of analgesics. Recovery occurs usually within 1–2 months, with sequelae in up to 10% of cases.[65] Although the exact pathophysiological mechanism is unknown, the sudden onset of some tendinopathies suggests a direct toxic effect of fluoroquinolones on tendons, possibly by inducing apoptosis of tendon cells.[69]

More than 40 years ago, the first case reports linked the use of corticosteroids with the occurrence of tendinopathies, mainly tendon ruptures.[70] According to a recent analysis of published and spontaneous reports involving 324 patients, oral and parenteral applications, especially intra-articular use, were the most prevalent routes of administration in cases of corticosteroid-associated tendon disorders.[70] Both inhaled and topically applied corticosteroids might also be rarely associated with tendinopathies.[70] Achilles and patellar tendinopathies accounted for almost 70% of published cases.[70] However, it was often difficult to assess a causal relationship between corticosteroid exposure and tendinopathy because of the presence of confounding factors.[70] In fact, there was often an underlying disease that *per se* could predispose to tendinopathy.[70]

There is some evidence that statins and fibrates may occasionally induce mild tendonitis, of which the symptoms completely resolve within 1–2 months after discontinuation of the culprit drug.[71] However, it should be remembered that tendinopathies, presumably due to lipid deposits within tendons, may be a clinical feature of certain types of hyperlipidaemia.

Retinoids too have been incriminated in the occurrence of tendinopathies.[72] However, most periarticular disorders associated with retinoid use involve the entheses, i.e. the areas at which tendons, ligaments and articular capsules insert into bone.[73]

4.2 Enthesopathies

Isotretinoin and acitretin, the major metabolite of etretinate, are vitamin A derivatives widely used in the treatment of several chronic dermatoses. In common with chronic hypervitaminosis A, long-term use of synthetic retinoids may cause ossifying enthesopathy resembling diffuse idiopathic skeletal hyperostosis or Forestier's disease.[73] Patients may be asymptomatic or complain of pain, stiffness and decreased range of motion in the affected areas.[73] Symptoms are poorly correlated with radiographic findings.[73] These include axial and/or peripheral ossification enthesopathy with calcification of the anterior and posterior longitudinal vertebral ligaments.[73,74] Hyperostoses occur more often in the axial skeleton with isotretinoin and with greater frequency appendicularly with acitretin therapy.[73,74] The radiographic abnormalities are dose- and time-related.[1,74] They stabilise after treatment discontinuation.[1,74]

Periosteal new bone formation and, in children, growth retardation and premature epiphyseal plate closure have also been noted in a few instances.[1,73]

4.3 Periarticular Calcifications

Periarticular calcifications may be seen on radiographs several months after intra-articular corticosteroid injections, particularly of the finger joints.[75] These lesions are usually asymptomatic and even disappear with time.[1,75]

Intradiscal corticosteroid therapy that had been proposed for the treatment of discogenic back pain or sciatica secondary to herniated nucleus pulposus, may accelerate degeneration within the disc space and cause local calcifications.[1,76] These changes may result in worsening of back pain and nerve root compression.[1] Thus, intradiscal corticosteroid injections should no longer be performed in as much

as they have not proven effective in patients with discogenic back pain.[76]

4.4 Frozen Shoulder

Frozen shoulder, or 'adhesive capsulitis', is a painful and disabling condition characterised by limitation of active and passive motion of the shoulder joint.[77] The process usually resolves spontaneously within 1–3 years, but ultimate resolution may not be complete.[77] The pathogenesis of this condition remains elusive, but it may be a form of reflex sympathetic dystrophy, also known as complex regional pain syndrome.[78]

Drugs implicated in the development of frozen shoulder include protease inhibitors used for HIV infection,[79] fluoroquinolones,[80] isoniazid and antiepileptic drugs, particularly barbiturates.[1,81] Isoniazid and barbiturates have been incriminated in the occurrence of the so-called shoulder-hand syndrome, which combines a complex regional pain syndrome of the hand and wrist with frozen shoulder.[1,81]

The immunosuppressive agents ciclosporin and tacrolimus would also appear to induce a symmetrical epiphyseal pain syndrome and reflex sympathetic dystrophy of the lower limbs in transplant patients.[1,82] These patients had generally high blood concentrations of ciclosporin or tacrolimus, and they improved when the drug doses went down, suggesting that these adverse events could be prevented by close monitoring of drug concentrations.[1,82]

5. Bone Disorders

As previously mentioned, drugs such as bisphosphonates, granulocyte colony stimulating factors, ciclosporin and tacrolimus may cause nonspecific bone pain. Others may induce well defined bone disorders.

5.1 Osteoporosis

5.1.1 Corticosteroids

Prolonged administration of corticosteroids is the leading secondary cause of osteoporosis today.[83] This complication is predictable and preventable at once.

The classical mechanisms underlying the detrimental effects of glucocorticosteroids on bone include: (i) direct inhibitory effects on osteoblast function, (ii) reduction in the production of estrogen and testosterone along with inhibition of the osteoanabolic action of sex steroids; and (iii) enhanced effects of parathyroid hormone.[83,84] It has also been suggested that glucocorticosteroids lead to a negative calcium balance, thereby promoting secondary hyperparathyroidism.[3] However, whether this mechanism contributes to osteoporosis is controversial.[83,84] More recent findings indicate that glucocorticosteroids inhibit osteoblastogenesis and osteoclastogenesis, and reduce the lifespan of osteoblasts and osteocytes.[84] In summary, current data support the view that the direct effects of corticosteroids on bone cell proliferation and function and apoptosis are the major contributory mechanisms in the pathogenesis of osteoporosis.[83,84]

By reducing bone formation and increasing bone resorption, glucocorticoid therapy may result in a quantitative (bone loss) as well as qualitative (reduction in mechanical stability) defect of bone.[83,84] Consequently, the rates of fractures in patients receiving corticosteroids are higher than would be expected from measurement of bone mineral density, which merely estimates bone mass.[85-87]

Since trabecular bone is more susceptible to the negative effects of glucocorticoids than cortical bone, fractures affecting the vertebrae and, to a lesser extent, the ribs and pelvis are particularly prevalent.[83] However, oral corticosteroids have also been shown to confer an increased risk of hip fracture.[87-89]

The risk for developing osteoporosis appears to be variable and depends on a number of factors, including individual susceptibility, systemic exposure to corticosteroids, age and menopausal status.[83] Based on data obtained from the UK General Practice Research database[90] and two randomised clinical trials,[86] the increased risk of fracture appeared to be more strongly related to daily dose than to cumulative dose of oral corticosteroids. Although

young people lose bone more rapidly than older people, fracture rates are greater among patients who already have low bone mass, such as postmenopausal women and elderly patients.[83,86] Of note, inhaled glucocorticoids do not appear to pose a hazard to significant bone loss,[91] or an increased rate of hip fracture in elderly women.[92]

Any patient for whom oral glucocorticoid therapy at a minimum daily dose of 5–7.5mg of prednisone is anticipated to be required for >3 months should be assessed for his risk of developing osteoporosis.[83,93-95] Since calcium and vitamin D supplementation has been shown to prevent bone loss in patients starting glucocorticoids, this treatment may be used as first-line therapy in patients with no risk factors and normal bone mineral density at baseline.[93] However, current guidelines usually recommend oral bisphosphonates, such as alendronic acid or risedronic acid as first-choice therapy for the prevention and treatment of glucocorticosteroid-induced osteoporosis.[94,95] Therapies to prevent bone loss should be initiated at the start of corticosteroid treatment because the largest reduction in bone mass occurs in the first 6–12 months after starting corticosteroids, and the risk of fracture occurs early in the course of corticosteroid treatment.[83,93] However, secondary prevention in patients receiving long-term corticosteroids will also reduce the fracture risk.[93] Additional preventive measures should include smoking cessation, limitation in alcohol consumption, weight-bearing exercise and prevention of falls.[83,94]

5.1.2 Anticoagulants

Experimental studies showed that heparins, unlike fondaparinux, exert a negative effect on bone metabolism.[96] About 2–3% of patients receiving long-term unfractionated heparin therapy will experience symptomatic vertebral fractures, and significant reduction in bone density will occur in up to 30%.[96] Symptomatic bone disease usually occurs with a daily dose >10 000U given for >3 months.[96,97] Controlled clinical trials showed that patients receiving long-term low-molecular weight heparins were less likely to develop osteoporosis or fractures than those receiving unfractionated heparin.[96]

Vitamin K allows for γ-carboxylation of glutamyl residues, a conversion that activates clotting factors and bone proteins.[98] Since vitamin K antagonists inhibit this process, they were thought to lead to osteoporosis. However, retrospective observational studies of oral anticoagulant use and bone mineral density produced conflicting results.[99] A prospective cohort study involving 6201 elderly, postmenopausal women showed that regular use of warfarin was not associated with greater bone loss or increased risk for fracture of the hip or heel compared with nonusers.[99] These findings have been confirmed by a recently published retrospective cohort study.[98] Nevertheless, this study suggested that long-term warfarin therapy (≥1 year) was significantly associated with osteoporotic fractures in elderly men (OR 1.63; 95% CI 1.26, 2.10).[98] Finally, the decrease in bone mineral density was reported to be less pronounced in patients receiving prolonged treatment with the vitamin K antagonist acenocoumarol compared with those given the low-molecular weight heparin enoxaparin sodium.[100]

5.1.3 Drugs Used in Hormone-Dependent Cancers

Androgen deprivation therapy with GnRH analogues has become a standard treatment for advanced prostate cancer.[101] These drugs are also used in women with endocrine-responsive breast cancer and other sex hormone-dependent disorders. After repeated administration of GnRH analogues in premenopausal women, estradiol levels are reduced to close to postmenopausal levels.[102] Similarly, the levels of testosterone fall to castration values in men. The resulting hypogonadism after GnRH therapy leads to increased bone turnover, significant bone loss, and increased risk of fractures. As many as 19.4% of men surviving at least 5 years after diagnosis of prostate cancer have a fracture if treated with androgen deprivation therapy compared with 12.6% of controls.[101] Vitamin D deficiency exacerbates the development of osteoporosis, so vitamin D status should be evaluated before commencing GnRH analogues, and adequate calcium and vitamin D supplementation should be provided throughout

treatment.[101] Finally, bone mineral density should be monitored in these patients, and bisphosphonate therapy should be considered in patients with established osteoporosis.[101]

The third-generation aromatase inhibitors are being increasingly used in patients with breast cancer. Since peripheral aromatase activity is a major source of estrogens in postmenopausal women, it is hardly surprising that aromatase inhibitors drastically depress estrogen levels in this population.[102] Consequently, aromatase inhibitors may have detrimental effects on bone. A long-term, double-blind, randomised trial that compared tamoxifen with the aromatase inhibitor anastrozole in 9366 postmenopausal women with localised breast cancer showed that the former was associated with fewer fractures and arthralgia than was the latter.[103] Fracture rate per 1000 woman-years were 22.6 for anastrozole and 15.6 for tamoxifen (hazard ratio 1.44; 95% CI 1.21, 1.68).[103] Conversely, anastrozole was more effective and, in many respects, better tolerated than tamoxifen.[103]

Megestrol, a progestational agent for the treatment of metastatic breast cancer and endometrial cancer, may also contribute to the development of osteoporosis and subsequent fractures.[104]

5.1.4 Methotrexate

The term 'methotrexate osteopathy' was first used to refer to a clinical syndrome characterised by diffuse bone pain, osteoporosis, and stress fractures of the lower extremities in children who had been placed on long-term maintenance therapy with low-dose methotrexate for acute lymphoblastic leukaemia.[105] There have also been sporadic reports of similar cases among patients receiving low-dose methotrexate for rheumatic diseases, primarily rheumatoid arthritis.[105] Although methotrexate may exhibit negative effects on bone mass and inhibit fracture healing in animals, it was not shown to affect bone mineral density in rheumatoid patients.[105] Since this osteopathy may develop within 3–4 months of treatment and appears to be unrelated to both weekly and cumulative doses of methotrexate, it may be a form of idiosyncratic adverse reaction.[106]

5.1.5 Drugs Acting on the CNS

Several categories of drugs acting on the CNS have been reported to be associated with an increased hazard of fracture in the elderly.[107,108] Several mechanisms could account for the association. Anxiolytics or hypnotics, antidepressants and possibly opioids might cause fractures by elevating the risk of falling.[107-111] Furthermore, a cross-sectional survey suggested that opioid and antiepileptic drugs, primarily phenobarbital, may be associated with fracture through reducing bone mineral density.[108] The association between exposure to opioids and decrease in bone mass may be by inhibiting endogenous sex hormone production and interfering with bone formation.[108] Antiepileptic drugs will be considered in a further detail (see section 5.2).

A small cross-sectional survey suggested that patients with schizophrenia receiving long-term conventional prolactin-raising antipsychotics (e.g. risperidone, haloperidol, chlorpromazine) had higher rates of low bone mineral density values than those given the prolactin-sparing antipsychotic olanzapine.[112] However, in a further larger study, the mean bone mineral density showed no clinically significant reduction in patients receiving long-term therapy with antipsychotics compared with matched controls.[113] Furthermore, bone mineral density was not correlated with prolactin levels in these patients.[113]

5.1.6 Vitamin A

Since experimental studies indicate that hypervitaminosis A is associated with increased bone resorption along with reduced bone formation, excessive intake of vitamin A (retinol) has been postulated to contribute to the development of osteoporosis in humans.[114] A recent review of published clinical studies evaluating the effects of vitamin A on bone has suggested a potential inverse relationship between excess vitamin A consumption and bone mineral density leading to an increased risk for fracture.[114] Although current data are limited, patients should be made aware of the potential risks of consuming vitamin A in amounts exceeding the recommended dietary allowance.[114]

5.2 Vitamin D Deficiency and Osteomalacia

Persistent vitamin D deficiency may result in osteomalacia, i.e. defect in the mineralisation of the newly formed matrix in the adult skeleton, thereby contributing to skeletal fragility.[2]

It was classically accepted that long-term treatment with medications inducing the cytochrome P450 (CYP) enzyme system (e.g. rifampicin and antiepileptic drugs) may produce rickets in children and osteomalacia in susceptible adults, such as institutionalised persons and older women, via increased catabolism of vitamin D.[2,97] Several studies reported that serum levels of 25-hydroxy-vitamin D, the commonly used index for vitamin D status, were decreased in patients receiving prolonged treatment with phenytoin, phenobarbital or carbamazepine, the lowest levels having been observed in patients receiving polytherapy.[115] Biochemical abnormalities and histological findings consistent with osteomalacia have also been reported in patients receiving long-term antiepileptic drug therapy.[97,115] Conversely, a prospective study showed that long-term treatment with antiepileptic agents in young male patients with epilepsy caused significant bone loss at the hip in the absence of vitamin D deficiency.[116] Furthermore, emerging data suggest that valproate, an enzyme inhibitor, may also affect bone.[117] Thus, it is likely that antiepileptic drugs can cause bone loss without inducing vitamin D deficiency-induced osteomalacia.[115-117] These drugs may lead to osteoporosis by increasing bone turnover.[115-117]

Whatever the mechanism, a prospective cohort study indicated that continuous antiepileptic drug use, particularly phenytoin use was associated with increased bone loss at the calcaneus and hip in elderly women.[118] As a result, the risk of hip fracture may be increased by 29% over 5 years in this population.[118] Preventive measures should include adequate calcium and vitamin D intake, and dual energy x-ray absorptiometry scanning of the hip to identify patients at increased risk for fracture.[115-118]

For etidronate, a first generation bisphosphonate, the dose that inhibits bone resorption *in vivo* is very close to that which impairs normal mineralisation, and this may lead to the development of osteomalacia.[52] Painful fissure fractures were mainly observed in patients with Paget's disease of bone or fibrous dysplasia of bone who were given etidronate at daily doses above 10 mg/kg for periods >6–12 months.[52,97] On the other hand, the use of low intermittent doses of etidronate for the treatment of osteoporosis does not lead to osteomalacia.[52] Similarly, the currently used second- and third-generation bisphosphonates are virtually devoid of the risk of impaired mineralisation and subsequent stress fractures.[3,52,97]

Since sodium fluoride appeared to stimulate bone formation, it had been used for the treatment of postmenopausal osteoporosis in some countries. Unfortunately, the newly formed bone was of abnormal quality, exhibiting defective mineralisation and osteomalacia.[2,97] Accordingly, stress fractures were a common adverse effect of fluoride therapy.[2,3,97]

Patients with chronic renal failure receiving long-term treatment with aluminium-containing antacids may develop aluminium osteopathy.[2,97] This condition is associated with variable histological changes, including osteomalacia.[97]

5.3 Osteonecrosis

It is well established that high-dose systemic corticosteroid therapy is a significant risk factor for avascular osteonecrosis.[119] The condition most commonly affects the femoral head, and bilateral involvement is not infrequent. Using magnetic resonance imaging, osteonecrosis could usually be detected within the first 4 months after starting high-dose corticosteroid treatment, whereas joint pain may be absent for a long time.[120,121] Of note, osteonecrosis may develop following brief courses (≤7 days) of high-dose corticosteroid medication.[120] Osteonecrosis may lead to subsequent collapse and secondary osteoarthritis of the affected joint. Intravascular coagulation may play a role in the pathogenesis of osteonecrosis. It has been hypothesised that high-dose corticosteroid treatment may enhance the development of osteonecrosis as a result of microvascular ischaemia in patients with SLE who have vasculitis.[121] Furthermore, a genetic predisposition to corticosteroid-induced osteonecrosis has

been demonstrated in kidney transplant patients.[119] Whether low-dose oral corticosteroid too may lead to osteonecrosis remains controversial. According to a large retrospective cohort study, patients with rheumatoid arthritis were found to develop two forms of femoral head osteonecrosis, the classic avascular form and a degenerative form.[122] Both forms were significantly associated with corticosteroid use, suggesting that low-dose corticosteroid therapy does not protect rheumatoid patients against the development of osteonecrosis.[122]

Cancer patients receiving long-term treatment with intravenous pamidronic acid and zoledronic acid may develop osteonecrosis of the jaw.[123-125] Several similar cases have also been observed in patients receiving long-term oral aminobisphosphonate, particularly alendronic acid, for osteoporosis.[123,124] The disorder was more frequent and occurred earlier in patients given zoledronic acid than in those given pamidronic acid or alendronic acid.[124,125] In that respect, the mean time to onset of osteonecrosis among patients receiving zoledronic acid was reported to be 9.4 months in one study[124] and 18 months in another.[125] A history of underlying dental problems, such as tooth removal or infection was present in more than two-thirds of patients with osteonecrosis.[124,125] Consequently, dental care is recommended before starting intravenous aminobisphosphonate therapy in cancer patients.[124] Furthermore, dental surgery should be avoided during bisphosphonate therapy.[124]

An increasing number of reports documents a relationship between HIV infection and osteonecrosis.[119] There is conflicting evidence relating antiretroviral therapy, particularly protease inhibitors, to the development of osteonecrosis because many patients had numerous risks factors already associated with osteonecrosis.[119]

6. Myopathies

Although many drugs may induce myalgia, only a limited number have been incriminated in the occurrence of well defined myopathies.[4]

6.1 Lipid-Lowering Drugs

It is well known that nicotinic acid, fibrates and statins may cause varying muscle disorders; severity varies from trivial myalgias or creatine kinase (CK) elevation in asymptomatic individuals to life-threatening rhabdomyolysis with myoglobinuria and subsequent acute renal failure.[126] Symptoms of clinically significant myopathies include any combination of myalgias, muscle weakness, or muscle tenderness.[126] The distribution of symptoms may be proximal, generalised, or regional.[126] The levels of serum CK can be normal as well as more or less elevated.[126,127] Rhabdomyolysis has been arbitrarily defined as markedly elevated CK levels with an elevated creatinine level consistent with pigment induced nephropathy.[127]

The literature on incidence of muscle disorders associated with lipid-lowering agents is confusing, in part because of a lack of clear definitions.[127] Myopathy is estimated to occur in approximately 0.1–0.3% of patients who receive statin monotherapy,[128] whereas up to 1–5% of patients may complain of muscle pain and weakness.[127] A retrospective cohort study estimated the incidence of hospitalised rhabdomyolysis in patients receiving lipid-lowering drug monotherapy at 0.44 (95% CI 0.20, 0.84) per 10 000 person-years for atorvastatin, pravastatin or simvastatin and 2.82 (95% CI 0.58, 8.24) for fibrates.[129] Using databases from the US FDA and National Prescription Audit Plus, the incidence of fatal rhabdomyolysis was estimated at 0.15 deaths per 1 million prescriptions of statins.[127] In view of the poor reporting of adverse drug events, the actual rate was most probably higher. Cerivastatin was more likely to induce rhabdomyolysis than other statins, and was consequently removed from the market.[4,127,129]

Known risk factors for the development of fibrate- or statin-associated myopathy include high doses, older age, and coexisting diseases associated with myopathy, such as renal insufficiency, hepatic dysfunction, diabetes mellitus and hypothyroidism. Furthermore, co-administration of fibrates or, to a lesser extent, nicotinic acid increases the risk for statin-induced myopathy.[4,126-130] Finally, concur-

rent use of statins that are metabolised via the CYP3A4 pathway (e.g. atorvastatin, lovastatin, simvastatin) and other agents that are potent inhibitors or substrates of this enzyme (e.g. ciclosporin, some macrolide antibacterials, azole antifungals, protease inhibitors and calcium channel antagonists) predisposes to myopathy.[4,126-130]

Lipid-lowering drug-induced myopathies may develop within several weeks to years after start of therapy.[4,130] Patients usually experience full resolution of muscle symptoms on cessation of the offending drug.[4,130] Of note, cross-intolerance between different drugs of the same class may occur.[4] After an episode of statin-associated myopathy, about half the patients would experience recurrent muscle pain on rechallenge with another statin.[130]

6.2 Corticosteroids

Prolonged use of corticosteroids may be responsible for a form of painless myopathy that is characterised by weakness and atrophy of the proximal musculature, primarily in the pelvic girdle.[4] This disorder usually develops in a few weeks or months according to the dose and nature of the agent, the fluorinated derivatives (e.g. triamcinolone and dexamethasone) being the most harmful.[4] Myopathy is uncommon in the setting of low-dose corticosteroid treatment. Among 175 patients with polymyalgia rheumatica treated with an average daily dose of prednisone 9.6mg for a mean duration of 2.4 years, 5 (2.9%) experienced this adverse event versus one patient out of 57 (1.8%) receiving NSAIDs alone.[131] No myopathy was recorded among 112 patients with rheumatoid arthritis on low-dose prednisone (<15 mg/day) for several years.[132]

The diagnosis may be difficult because muscle weakness and/or atrophy is a common feature of many rheumatic diseases for which corticosteroids are employed.[4] Further confounders may be corticosteroid-induced hypokalaemia and muscle weakness related to DMARDs, such as antimalarial agents.[4] Evidence in favour of corticosteroid-associated myopathy is the symmetric and typically painless nature of the myopathy, without any neurological signs, normal plasma electrolytes and CK levels, and improvement after tapering corticosteroid dosage.[4]

6.3 Antimalarial Agents

When prescribed at high doses as DMARDs, chloroquine and, to a lesser extent, hydroxychloroquine may induce myopathy and even neuromyopathy, which develop in an insidious manner.[4] This complication is virtually never observed within the first 6 months of treatment.[133]

Initial symptoms are characteristically mild and may be masked by the musculoskeletal manifestations of the underlying disease so the diagnosis is often delayed.[133] Painless proximal weakness in both the upper and lower extremities may become more severe with time.[133] A slight increase in serum muscle enzymes, especially lactate dehydrogenase may be observed.[133] The outcome is favourable in the 3–6 months following discontinuation of the culprit drug but recovery may be incomplete.[4]

A retrospective chart review suggested that the incidence of clinical myopathy in rheumatic patients treated with these antimalarials was 1 in 100 patient-years (95% CI 0.2, 3.0).[134] A 3-year prospective longitudinal study showed a prevalence of clinical myopathy of 6.7% among 119 patients with rheumatic diseases treated with the same antimalarials.[133]

6.4 Colchicine

Patients taking therapeutic dosages of colchicine over a prolonged period of time may develop a subacute, often severe, proximal myopathy in conjunction with a relatively mild polyneuropathy.[4] The patients present with proximal muscle weakness with distal areflexia, minor sensory loss and elevated serum CK levels.[4] Rhabdomyolysis is exceedingly rare in patients receiving low-dose colchicine.[135] Myopathies as a result of colchicine therapy occur mostly in patients with renal failure.[4] Concomitant ciclosporin therapy may also increase the risk of colchicine myotoxicity.[135]

6.5 Nucleoside-Analogue Reverse Transcriptase Inhibitors

The prolonged use of zidovudine may induce a particular variety of reversible mitochondrial myopathy, which is usually painful, with pronounced wasting and tenderness.[4] Muscle weakness predominantly affects the proximal musculature. Serum CK levels are normal or mildly elevated.[4] This disorder is theoretically distinct from HIV myositis, in which pain and tenderness are usually absent.[4] However, a distinction between these two entities seems impossible in many cases.[4] The fact that other nucleoside-analogue reverse transcriptase inhibitors may also induce myopathy is suggestive of a class effect.[4]

It is noteworthy that these agents may be responsible for hyperlactataemia syndromes, possibly via inhibition of mitochondrial DNA polymerase.[136] In a very few cases, these syndromes were accompanied by toxicities believed to have a mitochondrial basis, including myopathy.[136]

7. Conclusion

In view of the broad spectrum of drug-related musculoskeletal disorders and a vast array of incriminated drugs, any new rheumatic symptoms or syndromes should be regarded as possibly related to drug treatment. Furthermore, information of the patients along with appropriate preventive measures and/or monitoring should be considered when prescribing drugs or drug classes with well appreciated risks for musculoskeletal symptoms or syndromes.

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