



Rheumatic manifestations of endocrine disease

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Purpose of review

Musculoskeletal complaints are a feature of several endocrine diseases. This review will update clinicians on their association, presentation, and treatment.

Recent findings

To update clinicians on the recent literature as it is related to pathophysiology, genetic, and clinical findings on the association of these diseases and musculoskeletal complaints.

Summary

Rheumatologists in the clinic are faced with different presentations of various musculoskeletal complaints every day. Every new patient encounter requires the differential diagnosis of these complaints. The first task is usually to decide with what disease in internal medicine these complaints are associated. The endocrinopathies are a group of illnesses that either present initially or exhibit sometime during the course of the disease as a variety of musculoskeletal complaints. Rheumatic manifestations may often be the initial presentation of an endocrine disorder. Each endocrine disorder may also have its own arthritic complaints, which can present as a definitive rheumatic disease such as calcium pyrophosphate dihydrate deposition disease or as a rheumatic symptom such as diffuse arthralgia. The rheumatologist as well as the primary care physician should be knowledgeable about the ways in which muscles, tendons, ligaments, and joints are affected by diseases of the endocrine system.

Keywords

arthritis, diabetes mellitus, endocrine, parathyroid, pituitary, thyroid

INTRODUCTION

Rheumatic manifestations are often the initial presentation of systemic illnesses. Each endocrine disorder has its own set of arthritic complaints that can often mimic or present as definitive rheumatic diatheses, such as calcium pyrophosphate dihydrate deposition (CPPD) or diffuse arthralgia. Both rheumatologists and primary care internists should be well versed in identifying the manner in which components of the musculoskeletal system are affected by diseases of the endocrine system. This article seeks to build upon a prior review done on the subject [1], by updating the reader on what is new about these manifestations, as well as advances in genetic analyses and available therapeutic options.

THYROID DISORDERS

Hypothyroidism often presents with a characteristic symmetrical arthropathy involving stiffness of the joints of the hands and knees. On palpation the joints feel 'gelatinous' and aspiration of fluid is usually non-inflammatory, viscous, and high levels of hyaluronic acid and CPPD crystals can often be found [2]. A myopathy has also been reported with

hypothyroidism, usually presenting with proximal weakness and fatigue, normal creatinine phosphokinase (CPK) levels, normal muscle pathology on biopsy, and hypercholesterolemia [3,4].

Carpal tunnel syndrome may present as an initial manifestation of hypothyroidism in upwards of 7% of patients [5]. Hyperthyroidism (Graves' disease) presents with pretibial myxedema usually associated with Graves' ophthalmopathy. The myxedema may appear as nodules which vary in size from 1 cm to large lesions covering most of the pretibial surface, and colored from pink to a light purple hue.

Patients with hyperthyroidism may have associated proximal muscle weakness (associated shoulder adhesive capsulitis), loss of muscle mass, and weight loss. However, most of these manifestations correct

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KEY POINTS

- Endocrine disorders can initially present or manifest during the course of rheumatic diseases with a multitude of musculoskeletal complaints.
- Endocrine manifestations of underlying autoimmune disorders can occur commonly and need to be promptly recognized.
- Advances in genetic analyses through genome-wide association study (GWAS), as well as an emerging understanding of the effects of nonbiologic/biologic disease-modifying antirheumatic drugs (DMARDs) on endocrine manifestations in autoimmune diatheses, can potentially guide clinicians in selecting targeted, appropriate therapies in the future.

with treatment [6]. A common and serious manifestation of hyperthyroidism is osteopenia and osteoporosis. Treating to a targeted normal thyroid-stimulating hormone (TSH) level, as well as adjusting the dose of thyroid replacement as needed in hypothyroid patients, is critical. Additionally, improvement in bone mineral density (as measured by densitometry) in patients with thyroid disease is essential [7,8].

THYROID DISORDERS IN PATIENTS WITH CONNECTIVE TISSUE DISEASE

The occurrence of chronic autoimmune thyroiditis (Hashimoto's thyroiditis) as well as hypothyroidism is common in the general population [9], making it difficult to ascertain whether the incidence of either is increased in patients with connective tissue disease. Two exceptions appear to be scleroderma in which fibrosis is the cause of hypothyroidism and congenital heart block in children of hypothyroid anti-Ro mothers. A common reason for referral to a rheumatologist is often a young female patient with arthralgia in whom the referring physician has obtained serological testing positive for antinuclear antibody (ANA). Studies of patients with Graves' disease and chronic autoimmune thyroiditis have demonstrated upwards of 26% positivity for ANA and 34% positivity for antisingle-stranded DNA antibodies. No patient in these studies had antibodies to double-stranded DNA, or extractable nuclear antigens (anti-Ro/SSA, anti-La/SSB, anti-Smith, or anti-ribonucleoprotein) [10]. To evaluate the prevalence of chronic autoimmune thyroiditis or Hashimoto's thyroiditis in a group of patients with spondyloarthritis (SpA), serum levels of thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4), and titers of

antithyroglobulin and antithyroid peroxidase (anti-TPO) antibodies were assayed. Ultrasonography of the thyroid gland was performed in all patients and rheumatic activity was evaluated. Results of this study showed that indices of thyroid autoimmunity were significantly more frequent in patients with SpA than in controls and that in the SpA group, a higher prevalence of Hashimoto's thyroiditis was found in patients with active disease than in those with low-to-moderate disease levels. In the SpA group, patients with disease duration more than 2 years had a higher prevalence of Hashimoto's thyroiditis and positive anti-TPO antibodies than patients with a disease duration of 2 years or less. Ultrasonography detected a significantly higher frequency of thyroid nodules and hypoechoic pattern in patients with SpA than in controls. This study demonstrated a significantly higher prevalence of thyroid autoimmunity in patients with SpA compared with controls. In addition, thyroiditis appeared to occur more frequently in patients with longer disease duration and active rheumatic disease. It was suggested that routine thyroid function studies be part of a clinical evaluation in patients with SpA [11]. Additionally, chronic autoimmune thyroiditis (ATD) frequently overlaps with autoimmune disorders. Patients with ATD have been found to have a significantly higher prevalence of ANA than their healthy counterparts [with prevalence of ATD in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) being 24%] [12]. This suggests that it is clinically important to screen patients with SLE and RA for the coexistence of thyroid autoimmune disease [12].

HYPOPARATHYROIDISM

Hypoparathyroidism is a disorder in which parathyroid hormone (PTH) is deficient in circulation, most often due to immunological destruction of the parathyroid glands or their surgical removal. Seen infrequently, the clinical manifestations are a result of hypocalcemia. Albright's osteodystrophy or pseudohypoparathyroidism (pseudo HoPT) results from end-organ resistance (bone and kidney) to PTH and presents with elevated levels of PTH, hypocalcemia, and hyperphosphatemia. Type 1a HoPT (autosomal dominant) is inherited maternally and characterized by calcification of the perispinal ligaments, short stature, and mental retardation. Patients clinically have shortened metatarsal and metacarpal bones and a defect in the genes encoding the alpha subunit of the cell membrane-associated guanine nucleotide-stimulating unit of adenyl cyclase [13]. Type 1b HoPT also has resistance to PTH, but has a normal phenotype and is inherited paternally

[14,15]. Soft tissue calcifications not clinically relevant (in basal ganglia, cataracts, shoulder joints, or subcutaneous tissues of the hands) have been reported in HoPT and infrequently in pseudo HoPT [16]. Surgically induced HoPT may also be accompanied by muscle weakness usually related to the degree of hypocalcemia and responsive to treatment with vitamin D and calcium. Renal disease can result in crystal deposition disease, including monosodium urate, calcium pyrophosphate, and hydroxyapatite as a result of hyperphosphatemia from reduced glomerular filtration and secondary hyperparathyroidism [17]. Monosodium urate deposition results in acute gout seen more commonly in renal insufficiency. Gout is rare in patients on dialysis but can be seen after renal transplantation with decreased creatinine clearance, as well as use of cyclosporine. CPPD deposition is seen less in renal disease than gout or hydroxyapatite and is rare in dialysis. Hydroxyapatite deposition can cause acute synovitis and periarticular inflammation. Painful subcutaneous nodules or chronic asymptomatic nodules (uremic tumoral calcinosis) can also occur. Prevention is achieved through phosphate restriction, adequate dialysis, and oral phosphate-binding agents. Renal osteodystrophy is a result of osteomalacia, osteitis fibrosa cystica, osteosclerosis, aluminum toxicity, osteoporosis, and β 2-microglobulin amyloid deposition, and can present with bone pain, muscle wasting and myalgias, as well as bone fractures [18].

ANKYLOSING SPONDYLITIS-LIKE DISEASES AND DIFFUSE IDIOPATHIC SKELETAL HYPEROSTOSIS

The skeletal abnormalities of hypoparathyroidism are caused by calcification, which can simulate ankylosing spondylitis with clinical signs, including morning stiffness and changes in gait and posture [19]. Sacroiliitis is not usually observed, though it is the earliest manifestation in most patients with ankylosing spondylitis. The patterns of syndesmophytes in patients with hypoparathyroidism can resemble those of ankylosing spondylitis with origin from the vertebral margin and preserved disc space, but more often there is also involvement of the posterior paraspinal ligament. The pain is not responsive to immunosuppressive agents and non-steroidal anti-inflammatory drugs, but can resolve completely with calcitriol therapy [20]. Serum calcium may need to be included in the diagnostic work-up of patients with inflammatory back pain, especially if they present with atypical features as previously described. It is important to differentiate hypoparathyroid-related spondylitis from

ankylosing spondylitis because the management for the two disorders is markedly divergent. In fact, some pharmacotherapy used for ankylosing spondylitis, such as bisphosphonates, may actually worsen hypocalcemia. The mechanism underlying these skeletal changes in hypoparathyroidism is not well defined. Decreased intestinal calcium absorption caused by a defect in the action of 1,25-dihydroxyvitamin D [1,25(OH) D₂] has been suggested to play a role in a controlled study [21] of paravertebral ligamentous ossification. Spinal changes in hypoparathyroidism have also been described to be similar to those in diffuse idiopathic skeletal hyperostosis (DISH), which is characterized by ossification of the anterior longitudinal ligament of the spine and various extraspinal ligaments, but is rarely reported before 50 years of age. Okazaki *et al.* [22] suggested that the ossifying diathesis of paravertebral ligaments, which is the origin of DISH, might be initiated or aggravated by hypoparathyroidism.

DIABETES MELLITUS

A long-standing association between diabetes mellitus and several rheumatic syndromes exists, with severity of the former determining the extent of rheumatic manifestations. Involvement of the hands in diabetic patients is observed in over 30% of patients and can present in a myriad of forms, including trigger finger, flexor tenosynovitis, Dupuytren's contracture, and/or 'stiff hand' syndrome [23–26]. Incidentally, the onset of these manifestations often predicts increased renal, ophthalmological, and other complications of diabetes mellitus. Trigger finger results from the occurrence of flexor tenosynovitis, which drives proliferation of fibrous tissue in the tendon, particularly when the tendon passes through the fibrous ring or pulley. DeQuervain tenosynovitis entails the same mechanism at the radial styloid with thickening of the extensor pollicis brevis or the adductor pollicis longus tendon and occurs in 17–23% of patients with diabetes mellitus [27]. Dupuytren's contracture (palmer thickening of the flexor tendons) has been initially reported in 15–21% of diabetic patients [28]. A recent study [29] demonstrated positive results with injections of collagenase clostridium histolyticum for the treatment of Dupuytren's contracture. Finally, diabetic 'stiff hand' syndrome (or diabetic cheirarthropathy) – a fibrosing syndrome often resembling scleroderma – results in contractures at the metacarpophalangeal and proximal interphalangeal joints [23,30].

Patients with diabetes mellitus often present with a diabetic neuropathy and its associated arthropathy. The pathogenesis is believed to be

neurovascular, rather than neurotraumatic (resulting from decreased sensitivity of nerve endings) or reduced flow secondary to arterial sclerosis of small vessels [31]. Patients with diabetes have increased blood flow (secondary to neuropathy involving the sympathetic nervous system) to subchondral bone, resulting in increased osteoclastic activity and bone resorption. This occurs even in the absence of peripheral vascular disease, resulting in bone fatigue and disorganization. It appears radiographically as progression from localized osteopenia to osteolysis of subchondral bone, fragmentation of bone and cartilage (part of which may become embedded in synovial tissue), and sclerosis [32]. Joints involved in order of frequency include ankle, metatarsophalangeal and tarsometatarsal. This distribution differentiates diabetic arthropathy from *tabes dorsalis* in which the knee is more commonly involved. The pathogenic mechanism active in diabetes mellitus that can cause tissue damage is unknown. One possibility includes the role of advanced glycation end products binding to receptors for advanced glycation endproducts receptors (increased in diabetes and mediators both of inflammation and increased atherosclerosis) on chondrocytes, thereby up-regulating matrix metalloproteinases which are involved in inflammation [33–35].

An inter-connection between gout, hyperuricemia, and the metabolic syndrome exists. The metabolic syndrome can increase the risk for atherosclerotic cardiovascular disease (CVD) and type 2 diabetes. A prior study [36] looked at the relationship between gout and the development of type 2 diabetes by prospectively studying a cohort of 11 351 men from the Multiple Risk Factor Intervention Trial (MRFIT) and found that amongst men with a high cardiovascular risk, men with gout were at a higher future risk of developing type 2 diabetes independently of the other known risk factors. A more recent study [37^{***}] attempted to explore the causal relationship between gout and type 2 diabetes based on genetic evidence and a national outpatient database. Results showed a total of 334 single-nucleotide polymorphisms (SNPs) were significantly related to gout in genome-wide association study (GWAS) ($P < 10^{-7}$) and type 2 diabetes was the most significantly associated disease with gout as recognized by 36 gene symbols corresponding to the above significant SNPs [37^{***}]. The analysis of the national outpatient database showed that the overall incidence of type 2 diabetes was 1.50 cases per 1000 person-months among gout patients, which was higher than the overall incidence of gout (1.06 cases) among type 2 diabetes. The age-adjusted standardized incidence ratio of type 2 diabetes

among gout was 2.59 [95% confidence interval (CI) 2.42–2.78], whereas for gout among type 2 diabetes it was 1.61 (95% CI 1.48–1.74). The study [37^{***}] concluded that after excluding obesity and alcohol consumption behavior, patients with gout and type 2 diabetes shared the most common genetic factors and that a mutual inter-dependence on higher incidences was observed.

The concurrent manifestations of autoimmune diseases, such as RA and type 1 diabetes mellitus, have been previously observed. RA has been linked with the premature development of cardiovascular disease, which is related to the inflammatory burden and predisposes the development of atherosclerosis in these patients. Systemic inflammation has also been implicated in predisposing patients to develop type 2 diabetes mellitus and insulin resistance. Given that systemic inflammation is increased in RA, the prevalence of diabetes may also be concomitantly increased. However, data from the National Health and Nutrition Examination Study (NHANES) III [38] suggested no association between RA and diabetes mellitus. However, some shortcomings of this study included too few patients with RA and diabetes mellitus, a mix of mild and severe RA patients, as well as no distinction made between anticyclic citrullinated peptide (CCP) positive and negative RA patients, and finally, an overwhelming concentration of patients with type 2 diabetes mellitus.

Interestingly, one established genetic risk factor, the 620W allele of the protein tyrosine phosphate N22 (PTPN22) gene, is shared by both RA and type 1 diabetes mellitus. In a prior study [39], the presence of this association was explored utilizing the Swedish database. All patients had blood samples that were tested for antibodies to anti-CCP, rheumatoid factor, and the 620W PTPN22 risk allele. Type 1 diabetes mellitus was associated with an increased risk of RA [odds ratio (OR) 4.9, 95% CI 1.8–13.1]. This association was specific for anti-CCP positive RA patients (OR 7.3, 95% CI 2.7–20.0) and attenuated to an OR of 5.3 when looking further for the presence of the 620W PTPN22 allele (95% CI 1.5–18.7) [39]. The study [39] concluded that the association of RA and type 1 diabetes mellitus was limited and specific to one subset of RA patients (anti-CCP positive) and the risk in patients with type 1 diabetes mellitus of developing RA in later life was attributed partly to the presence of the 620W PTPN22 allele (implying a possible common pathway for both autoimmune disorders).

Other studies looking for a genetic locus for susceptibility to multiple autoimmune diseases have focused on the discovery that a common SNP, rs6822844p, was found in linkage

disequilibrium on chromosome 4q27 with genes *KIAA1109*, *Tenr*, *IL-2*, and *IL-21*. These genes have been reported to be a strong genetic factor in celiac disease in humans and type 1 diabetes mellitus in mice. In a study [40] of type 1 diabetic, RA, and control patients in a Dutch population, an association was found in the *KIAA1109/Tenr/IL-2/IL-21* gene region with type 1 diabetes mellitus and RA, implying that this locus could be a general risk factor for multiple autoimmune diseases.

Given the aforementioned association between diabetes mellitus and RA, as well as routine use of both nonbiologic and biologic disease-modifying antirheumatic drugs (DMARDs) in clinical practice, very recent studies have attempted to investigate whether DMARD therapy can effect incidence of concurrent diabetes mellitus in patients with underlying RA. In a prior study [41¹¹], a retrospective cohort of 1127 adult patients with newly diagnosed RA and no diabetes mellitus was investigated to determine a protective relationship between hydroxychloroquine use and decreased risk of diabetes mellitus. The multivariate adjusted hazard ratio for incident diabetes among hydroxychloroquine users was 0.29 (95% CI 0.09–0.95, $P=0.04$) compared with nonusers [41¹¹]. The authors concluded that there is potential benefit of hydroxychloroquine in attenuating the risk of diabetes in RA patients [41¹¹]. Another study [42¹²] sought to compare the risk of newly diagnosed diabetes mellitus in patients with RA or psoriasis based on use of a variety of nonbiologic DMARDs and anti-tumor necrosis factor (TNF) agents. A retrospective cohort study of 13 905 participants with a diagnosis of either RA or psoriasis on at least two visits was undertaken. The multivariate adjusted hazard ratios for diabetes mellitus were 0.62 (95% CI 0.42–0.91) for anti-TNF agents, 0.77 (95% CI, 0.53–1.13) for methotrexate, and 0.54 (95% CI, 0.36–0.80) for hydroxychloroquine compared with other nonbiologic DMARDs. Hence, the study investigators concluded that among patients with RA or psoriasis, the adjusted risk of diabetes mellitus was lower for individuals starting an anti-TNF agent or hydroxychloroquine compared with initiation of other nonbiologic DMARDs. In a more recent study [43¹³], investigators sought to examine the association of anti-TNF agent use and the risk of developing diabetes mellitus in a RA inception cohort. Results indicated that after adjusting for covariates, the hazard ratio for incident diabetes mellitus in anti-TNF agent users was 0.49 (95% CI 0.24–0.99, $P=0.049$) compared with never users [43¹³]. The authors concluded that in this inception RA cohort, anti-TNF agent use was associated with a 51% reduction in risk of developing diabetes mellitus

[43¹³]. In addition to anti-TNF agents, tocilizumab, a humanized monoclonal antibody against the IL-6 receptor, has also been the focus of investigation. In a prior study [44], measurement of insulin sensitivity, serum adipokine levels, and lipid parameters in humans before and after treatment with tocilizumab were undertaken. The study's results indicated that the homeostasis model assessment index for insulin resistance decreased significantly with treatment. Whereas leptin concentrations were not altered by inhibition of IL-6 signaling, adiponectin concentrations significantly increased, and hence, the leptin to adiponectin ratio, a novel marker for insulin resistance, was significantly decreased after treatment [44]. Serum triglycerides, low-density lipoprotein (LDL)-cholesterol, and high-density lipoprotein (HDL)-cholesterol tended to be increased, whereas lipoprotein (a) levels were significantly decreased. Thus, the study [44] concluded that inhibition of IL-6 signaling improves insulin sensitivity in patients with immunological disease, suggesting that elevated IL-6 levels in type 2 diabetic patients might be causally involved in the pathogenesis of insulin resistance. A more recent study [45¹⁴] buttressed these findings in part by demonstrating that glycosylated hemoglobin (HbA1c) decreased in diabetic patients with RA who were treated with tocilizumab. HbA1c levels decreased significantly after 6 months of tocilizumab treatment in the diabetic group [45¹⁴]. Therapeutic drugs for diabetes were also tapered in the diabetic group; in nondiabetic patients who were treated, HbA1c was also slightly decreased. To date, this has been the first study of the possible ameliorative effect of tocilizumab on HbA1c levels, though further studies establishing a possible mechanism for this link remain to be completed.

ADRENAL DISORDERS

In 1932, Harvey Cushing described several rheumatic conditions including osteoporosis, avascular necrosis, myopathy, and synovitis, later to be termed collectively as part of Cushing's syndrome. Similar findings are also seen in exogenous Cushing's secondary to widespread use of corticosteroids. Mechanisms include inhibition of collagen metabolism as well as decreased availability of calcium reported in several reviews [46]. Avascular necrosis generally occurs after prolonged use of corticosteroids, but can be observed even after discontinuation of steroids. Steroid myopathy can occur in patients treated with corticosteroids and presents as extreme muscle weakness and pain, most often pronounced around the pelvic girdle. Usually, a muscle biopsy demonstrates type 2 fiber atrophy,

whereas electromyography shows a myopathic picture. Muscle enzymes are usually not elevated and the condition gradually improves as corticosteroids are tapered or discontinued completely [47]. A similar picture has been reported in Cushing's disease [48]. As part of this clinical presentation, osteoporosis can be related to the dose and duration of disease; several treatment regimens reported include the use of calcium, vitamin D (D3), bisphosphonates, and teriparatide (recombinant PTH) [49,50].

ADDISON'S DISEASE

Patients with this syndrome rarely present and are often difficult to diagnose. Symptoms include weight loss, myalgia, fatigue, abdominal pain, nausea, hyperpigmentation, and hypotension. Addison's disease associated with connective tissue is also rare, but in contrast to older studies in which tuberculosis was the main cause, autoimmunity is now the primary cause [51]. Musculoskeletal complaints during an adrenal crisis can present as painful flexion contractures at the hips and knees, which resolve with intravenous crystalloid and corticosteroid administration [52]. More commonly, iatrogenic Addison's, as a result of abrupt withdrawal of exogenous steroids, can occur, with patients presenting with overt and sudden hypotension, salt wasting, and hyperkalemia. Treatment is somewhat controversial [53,54], but generally, stress doses of steroids (40–60 mg prednisone equivalent in intravenous form in the first 24 h, followed by tapering to the patient's baseline dosing) are administered [55].

CONCLUSION

The review has attempted to bring the reader up to date on not only the occurrence, presence, and pathophysiology of rheumatic complaints in endocrine disease, but newer information shaping our understanding of underlying genetic causes behind endocrine disorders and autoimmune disease, as well as effects of newer biologic DMARD therapy on manifestations of endocrine disease. Additionally, this article has pointed out the often overlapping nature of endocrine disorders presenting in patients with underlying autoimmune diatheses.

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Conflicts of interest

There are no relevant conflicts of interest or sources of funding for this article.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 149–150).

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