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Osteoarticular disorders of endocrine origin

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Endocrine diseases may present with musculoskeletal complaints, and their outcome, even after endocrine control, can be impaired by bone and joint disorders. All musculoskeletal structures, including bone, cartilage, synovium, tendons and ligaments, can be involved by some processes triggered by the endocrine disorder and its related disturbances of homeostasis, including that of growth factors. Endocrine disorders may account for 20–30% of all cases of osteopenia or osteoporosis in adults, the main causes being central and peripheral hypogonadism, endogenous and exogenous hypercorticism or hyperthyroidism, and primary hyperparathyroidism. The physician should be aware of these identifiable and treatable causes of bone loss when interpreting bone mineral density measurements. It is also valuable to evaluate bone status in patients diagnosed with these endocrine disorders. Specific bone therapeutic measures could be discussed. Other frequent musculoskeletal features include myopathy and joint and soft tissue involvement. Endocrine myopathy is frequent in most of the endocrine disorders and is non-specific since proximal painless muscle weakness associated with normal serum enzyme levels and an uncommonly encountered electromyogram myopathic pattern are present in these diseases. Soft tissue involvement is also a frequent consequence of acromegaly, hypothyroidism and diabetes mellitus. There is also a risk of nerve entrapment syndromes in these conditions. Specific arthropathies are the hallmark of acromegaly at the spinal and peripheral joints. Neuroarthropathies are a severe complication of diabetes mellitus as a result of infection, neuropathy and vasculopathy. In all these settings, the physician should be aware that endocrine disorders are part of the differential diagnosis and, conversely, that these articular and peri-articular lesions should be managed independently of the control of the underlying endocrine condition, a specific outcome being borne in mind.

Key words: carpal tunnel syndrome; arthropathies; CPPD crystal disease; chondrocalcinosis; endocrine myopathy; osteoporosis; hypogonadism; hypercorticism; hyperthyroidism; hypothyroidism; hyperparathyroidism; hypoparathyroidism; diabetes mellitus; acromegaly; growth hormone deficiency.
disturbances of homeostasis, including that of growth factors. Some osteoarticular disorders can be resolved or improved after treatment of the underlying endocrine disease. In many circumstances, however, the bone and the joint disorders follow their own course. We will attempt in this chapter to review the bone disorders and extra-osseous manifestations related to various endocrine diseases.

**BONE DISORDERS OF ENDOCRINE ORIGIN**

Several endocrine hormones have a major impact on bone remodelling through receptor-mediated and/or local factor-mediated actions on bone cells. The most frequent bone disorder of endocrine origin is bone loss, which affects a significant number of patients with acquired gonadal deficiency, hypercorticism, hyperparathyroidism or hyperthyroidism. This has important consequences in daily practice. First, endocrine disorders should be on the list of aetiologies for any patient diagnosed with osteopenia or osteoporosis. Second, bone mineral density (BMD) measurement is an important part of the investigation of these endocrinopathies. Finally, the presence and severity of the bone disease may have specific therapeutic implications.

**Hypogonadism**

Gonadal hormones play a key role in the control of bone homeostasis. Oestrogen deficiency in women and androgen deficiency in men are associated with an acceleration of bone turnover showing a disproportionate increase in resorption compared with formation. The resulting bone loss primarily affects trabecular bone and may cause low-impact vertebral or Colles’ fractures. Molecular and cellular mechanisms involve direct receptor-mediated alterations of bone cells (mainly osteoblasts since osteoclasts have not been proved to express a significant number of oestrogen receptors) and indirect pathways. Among the latter, oestrogen deficiency modifies the secretion of local factors such as cytokines and growth factors, as well as altering the expression of their receptors, leading to increased osteoclastic differentiation/activity and to decreased osteoblastic proliferation and matrix synthesis. Bone-forming cells also express androgen receptors, which could be the target of the mechanisms leading to increased bone loss in hypogonadic males. Recent data have pointed to a role for oestrogens in the control of bone growth/loss in males. Oestrogen receptor inactivating mutations and aromatase deficiency have been associated with a low bone mass that was corrected in one patient by oestrogen replacement therapy. Gonadal hormone deficiency could result from several pathological conditions, either congenital or acquired (Table 1). The most frequent clinical setting is pre-menopausal secondary amenorrhoea and subsequent bone loss, a condition recently reviewed by Miller and Klionski. Hyperprolactinaemic amenorrhoea is associated with low bone mass, especially in the lumbar spine. The effect of prolactin on bone cells and bone tissue has not been evaluated, but it is not thought to be the main mechanism because a lower bone mass has been found in women with amenorrhoea compared with eumenorrhoeic women with a similar prolactin level. Moreover, bone loss has been correlated to the duration of amenorrhoea in some studies but not all. These data are, for several reasons, highly relevant from the clinical point of view. First, hyperprolactinaemia represents about 25% of the causes of secondary amenorrhoea. Affected women may enter the menopause with severe pre-existing osteopenia or even develop established osteoporosis with fragility fractures at a young age. Finally, therapeutic interventions for
Table 1. Causes of gonadal hormone deficiency associated with low bone mass.

<table>
<thead>
<tr>
<th>Central (hypogonadotropic) hypogonadism</th>
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<tbody>
<tr>
<td>Acquired</td>
</tr>
<tr>
<td>Functional hypogonadotropic insufficiency</td>
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<tr>
<td>Hyperprolactinaemia</td>
</tr>
<tr>
<td>Nutritional disorders (anorexia nervosa)</td>
</tr>
<tr>
<td>Excessive physical activity/stress</td>
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<tr>
<td>Hypercortisolism</td>
</tr>
<tr>
<td>Drugs: GnRH agonists, glucocorticoids and anabolic androgens</td>
</tr>
<tr>
<td>Hypothalamic or hypothalamic tumours: craniopharyngiomas, adenomas and metastases</td>
</tr>
<tr>
<td>General diseases: sarcoidosis, histiocytosis and haemochromatosis</td>
</tr>
<tr>
<td>Post-partum hypophyseal necrosis (Shehan's syndrome)</td>
</tr>
<tr>
<td>Iatrogenic/traumatic: cranial trauma, post-surgery and post-radiotherapy</td>
</tr>
<tr>
<td>Congenital: mutations in the GnRH receptor, LH, FSH and KAL-1 (Kallman syndrome) genes</td>
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<th>Premature ovarian failure</th>
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<tr>
<td>Accelerated follicular apoptosis</td>
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<tr>
<td>X chromosome abnormalities: Turner syndrome, etc.</td>
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<tr>
<td>Iatrogenic: chemotherapy and radiotherapy</td>
</tr>
<tr>
<td>Failure of follicular maturation</td>
</tr>
<tr>
<td>FSH receptor and LH receptor mutations</td>
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<tr>
<td>Autoimmune</td>
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<table>
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<th>Testicular failure</th>
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<tr>
<td>Chromosomal abnormalities: Klinefelter's syndrome</td>
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<tr>
<td>Testicular abnormalities</td>
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<tr>
<td>Vanishing testis</td>
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<tr>
<td>Testicular dygenesis</td>
</tr>
<tr>
<td>Chemotherapy</td>
</tr>
<tr>
<td>External insults: infectious, ischaemic, trauma and toxins</td>
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<td>General disease: haemochromatosis, etc.</td>
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<th>Oestrogen receptor mutations and aromatase deficiency (men)</th>
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<tr>
<td>GnRH = gonadotrophin-releasing hormone; LH = luteinizing hormone; FSH = follicle-stimulating hormone.</td>
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hyperprolactinaemia with a restoration of the normal ovulatory cycle have been shown to increase bone mass. However, BMD is not usually normalized and does not constantly increase with dopamine agonist therapy. Oestrogen therapy or surgery are considered in some cases, but their effects on bone mass have not been evaluated.  

Excessive exercise or stress and anorexia nervosa are frequently associated with osteopenia. Several studies have demonstrated significant bone loss in amenorrhoeic female athletes, especially competition long-distance runners and ballet dancers, compared with their eumenorrhoeic counterparts. These data suggest that bone loss in these athletes is the result of gonadal hormone deficiency and cannot be prevented by exercise. It has, however, recently been reported that high-impact loading and muscular contraction during gymnastic training are associated with a higher bone mass, despite a higher prevalence of oligoamenorrhoea, compared with age-matched runners who have similar values for lean and fat body mass. Other factors could be involved in this functional hypothalamic amenorrhoea and consequent bone loss: weight loss (without anorexia nervosa) and alterations of body composition (decreased fat mass), eating disorders, hypercortisolism, lack of testosterone or acquired gonadorelin gonadotrophin-releasing hormone (GnRH) deficiency.

The pathophysiological mechanisms involved in anorexia nervosa are very similar, but hypogonadism is, in this situation, constant and particularly severe and prolonged.
The hormonal profiles resemble those of pre-pubertal and pubertal children. Profound bone loss has been consistently reported at all skeletal sites, predominantly in the trabecular bone-rich axial skeleton. A long duration of amenorrhea and an early onset of the disease (before the age of 18 years) are associated with a lower spinal bone density.

Interestingly, amenorrhoeic athletes are at increased risk of stress fractures but not of spinal compression fractures, in contrast to anorexia nervosa, in which vertebral fractures as well as non-spinal fractures have been reported. These differences probably reflect the particular severity of bone loss, hormonal disturbance and nutritional disorder in anorexia nervosa. A partial recovery of bone mass has been reported after resumption of the menses, the correction of nutritional disorders and weight recovery in both conditions. However, significant osteopenia may persist and could provide a rationale for a discussion of therapeutic intervention with either anti-osteoclastic or bone-forming agents.

Other causes of acquired hypogonadism include iatrogenic gonadotrophin deficiency. GnRH agonist therapy is used in young pre-menopausal women with severe endometriosis or uterine leiomyomas, or in men with prostate cancer. In both sexes, the chronic use of this treatment induces a rapid inhibition of gonadal hormone secretion, which is associated with high bone turnover or accelerated bone loss. For short-term (6-month) treatments, bone mass appears to recover at least partially after the cessation of GnRH. The effect of longer-duration or repeated sequences has not been carefully evaluated. Taken together, the data available suggest that GnRH agonist-induced bone loss might be a clinically relevant problem only in patients with pre-existing osteopenia.

**Hypercorticism**

Both endogenous (Cushing’s syndrome) and exogenous (long-term glucocorticoid therapy) excess of glucocorticoids (GCs) are established causes of osteoporosis. Cushing reported in the 1930s that osteoporosis and vertebral fractures were major clinical features in patients with excess GC. In a pioneering study evaluating the impact on bone of several endocrine disorders, Seeman et al observed marked vertebral osteopenia during hypercortisolism. Since then, a number of densitometric studies have documented the pattern of bone loss induced by GCs, especially iatrogenically. Recent prospective studies have demonstrated that trabecular bone loss starts soon after the initiation of GC therapy, peaks at a 5–15% loss within 6–10 months, and levels off thereafter to continue at a slower rate of 0.5–1.5% per year. GC-induced bone loss is related to the dose and duration of GC but the minimal deleterious dose is still a matter for debate. The widely held notion that low-dose GC therapy does not affect bone mass has been recently challenged, based on data from patients with Addison’s disease undergoing replacement therapy: a linear relationship was observed between lumbar spine mineral density and the dose of hydrocortisone in men but not in women.

In clinical practice, the measurement of BMD provides clear evidence of an interindividual variability of bone loss besides the differences in GC dosage and duration, the fundamental basis of this variability being unknown. A recent study has suggested that vitamin D receptors (VDR) genotypes may not be a useful tool for identifying patients at higher risk, but other genes could be involved and need to be assessed. Since the severity of bone loss could also not be predicted by measurements of the biochemical markers of bone turnover, each patient starting long-term (i.e. 3 or more months) therapy should be considered to be at risk. The highest-risk patients
include elderly people and post-menopausal women (because of pre-existing osteopenia), as well as patients taking a higher GC dosage or with underlying conditions or concomitant therapies worsening their bone loss. The reversibility of GC-induced bone loss is an important issue, but there is no convincing evidence that complete recovery occurs after the cessation of exposure, at least in adults exposed to high-dose exogenous hypercorticism. Only rare studies, most of them with a cross-sectional design, suggest that spinal BMD increases after a surgical cure of Cushing's syndrome. There is an urgent need to explore in greater depth, with a longitudinal follow-up of larger cohorts, the issues of variability and reversibility.

The pathophysiology of GC-induced osteoporosis has not been fully elucidated. Recent reviews provide a very comprehensive overview of all aspects of the actions of GCs on bone cells, bone tissues and other targets (for example, intestine and kidney) of mineral metabolism regulation.

Several drugs have been evaluated for their ability to prevent or to treat GC-induced bone loss. Most of these studies have been reviewed elsewhere, and we will focus here on clinical management. Treatment algorithms or recommendations have been proposed but are not yet fully validated. Recent controlled trials have yielded the general conclusion that bisphosphonates are nowadays the cornerstone of prevention and treatment. Both etidronate and alendronate have been shown to prevent bone loss in the lumbar spine and femoral neck. Although the number of patients involved in these trials suggests a cautious interpretation of fracture data, a decreased incidence of fractures was noted in treated patients compared with the placebo group. The high incidence of fractures in placebo-treated patients and the low number of patients needed-to-treat to prevent one osteoporotic fracture suggest that the prevention of bone loss with bisphosphonates is a cost-effective strategy when starting long-term (3-month or more), high-dose (10–15 mg or more per day) GC therapy. Other therapeutic measures include physiological calcium and vitamin D supplementation, hormone replacement therapy in post-menopausal women or patients with severe GC-induced hypogonadism, an improvement of physical activity, using the lowest possible dose of GC and local routes of administration, and a low-sodium diet to prevent or limit the calcium urinary loss. Bone densitometry has proved its usefulness in the diagnosis and clinical management of these patients.

**Thyroid disorders**

Thyroid hormones have a critical importance for bone growth and skeletal development. Tri-iodothyronine and thyroxine have been shown to increase bone resorption in vitro, but the mechanism of action at the cellular level is unknown, possibly being mediated partly by local prostaglandin secretion. At the tissue level, histomorphometric studies have shown that thyroid hormones increase the activation frequency of the bone remodelling sequence, shorten both the resorption and formation periods, but result in an imbalance between the two processes, with an excessive net resorption. As a result, the bone volume of both cortical and trabecular bone decreases with excess thyroid hormones.

The consequences for bone of a lack of thyroid hormones, i.e. hypothyroidism, have been very poorly evaluated. Osteosclerosis has been reported in infants with congenital myxoedema, and increased cortical volume and thickness or axial skeleton osteosclerosis have been noted in selected case reports. More systematic densitometric studies have, however, not demonstrated consistent changes in hypothyroid patients or differences in the rate of post-menopausal bone loss.
Endogenous hyperthyroidism (Graves' disease, toxic nodule or toxic multinodular goitre) is associated with a low BMD in most, but not all, studies. In a prospective epidemiological study of a large cohort of white women older than 65 years of age, a history of hyperthyroidism was associated with a 1.8 relative risk of hip fracture. BMD has been shown to increase in men and women treated successfully. It is therefore important, when managing a patient with hyperthyroidism, to monitor the BMD, to treat the thyroid disease in order to achieve a euthyroid state, and to consider treatment with a bone acting agent in patients with severe bone loss, fractures or associated risk factors (such as age and post-menopausal status).

The effect on bone of the exogenous suppression of thyroid-stimulating hormone (TSH) is a very controversial and sensitive issue. In an extensive search of the literature, Greenspan and Greenspan recorded 6 cross-sectional and 2 longitudinal studies in pre-menopausal women, and 7 cross-sectional and 3 longitudinal studies in post-menopausal women, showing that significant bone loss was associated with a partial or complete exogenous suppression of TSH. Although a roughly equal number of studies showed no effect of TSH suppression on bone, these authors recommend a bone mass measurement for women (the influence of L-thyroxine on bone being less impressive in men) who have been receiving thyroid hormones with full TSH suppression (e.g. to inhibit the progression or recurrence of differentiated hormone-dependent thyroid cancer). Anti-osteoclastic agents such as oestrogens or bisphosphonates could be considered, but calcitonin has not been shown to be efficacious. Thyroid hormone 'true' replacement therapy, i.e. the administration of a dose compensating a deficient secretion and maintaining a normal TSH level, seems not to have a deleterious effect on bone mass in most published studies. Therefore, standard measures for the diagnosis and management of osteoporosis apply to these patients, as in the general population.

There are several reasons to justify further research in this field. Thyroid hormone excess is clearly associated with osteoporosis and in some instances with metabolic complications such as hypercalciuria, renal stones or hypercalcaemia. Hyperthyroidism is the only endocrine disease demonstrated as a risk factor for osteoporotic fractures in older women. Exogenous L-thyroxine seems to affect BMD negatively in a dose-dependent manner. Larger controlled observational studies and therapeutic trials are urgently needed in order to improve our approach to the pathophysiology and clinical management of these patients.

**Parathyroid disorders**

Parathyroid hormone (PTH) modulates the bone remodelling sequence, primarily by acting on bone-forming cells that express a membrane receptor common for PTH and PTH-related peptide. The effects of PTH vary according to the concentration delivered, the rate of administration (continuous versus intermittent) and the bone site (trabecular versus cortical). The continuous administration and/or secretion of a large amount induces a high turnover state in the whole skeleton, with predominant resorption resulting in corticotrabeicular bone loss, focal osteolytic areas and subperiosteal erosions of small tubular bones. On the other hand, intermittent PTH selectively stimulates trabecular bone formation, supposedly by triggering the secretion of autocrine osteoblast growth factors such as insulin-like growth factors and transforming growth factor-β. According to the dose, and/or to other yet unknown factors, bone resorption may or may not be increased, especially in cortical sites. Besides bone, the main target organ of PTH is the kidney: PTH inhibits phosphate
reabsorption in the proximal tubule, stimulates the synthesis of calcitriol and increases calcium reabsorption in the distal tubule.

Hypoparathyroidism is a highly heterogenous clinical condition, characterized by chronic hypocalcaemia with frequent neuromuscular symptoms. The most frequent cause is thyroid or parathyroid surgery. Recent studies suggest a beneficial effect of chronic hypoparathyroidism on BMD and an attenuation of post-menopausal bone loss. The major goal of treatment is to maintain serum calcium within the normal range with calcium and vitamin D. High doses of 1,25-dihydroxyaminated vitamin D derivatives are necessary in some instances and require a careful monitoring of urinary calcium excretion and renal function. Favourable preliminary results have been obtained with synthetic human PTH 1–34 in 10 patients treated with either PTH injections or oral calcitriol.

Primary hyperparathyroidism (PHPT) is the third most common endocrine gland disorder after diabetes and thyroid disorders. Classical complications (osteitis fibrosa cystica and kidney stones) became uncommon as biological screening has expanded and as the measurement of plasma PTH level has become a precise and accessible diagnostic tool. The most common presentation is now asymptomatic mild hypercalcaemia, while patients may complain of rather non-specific symptoms (depression, fatigue, sleep abnormalities and constipation). The typical biological profile includes mild hypercalcaemia (of less than 2.67 mmol/l), a low or low-normal serum phosphate level and mildly elevated serum alkaline phosphatase. Several immunological dosages of intact PTH are currently used: the association of hypercalcaemia with an elevated or upper normal intact PTH level establishes the diagnosis. Bone involvement in PHPT can be detected by osteodensitometry. The increased availability of this technique is responsible for a more frequent diagnosis of PHPT in post-menopausal women with a low BMD. As discussed above, the dual skeletal actions of PTH on cortical and trabecular bone may be associated with a particular densitometric profile: the BMD may be preserved in the lumbar spine while decreased in the distal one-third of the radius and, to a lesser extent, in the hip. This should focus clinical investigations towards the diagnosis of PHPT.

Surgery is the only definitive treatment for PHPT, the success rate being over 90% in expert hands. Symptomatic PHPT patients are clearly candidates for surgery. The management of asymptomatic patients has been discussed in an important Consensus Development Conference, held at the National Institutes of Health in 1990, which recommended guidelines for the surgical or medical treatment of PHPT. A summary of the guidelines for surgery is listed in Table 2. Overall, about half of all patients meet the criteria. Pre-operative localization imaging (Sestamibi scanning, ultrasound, magnetic resonance imaging – MRI – or computed tomography – CT-scanning) is helpful only in patients who have had previous parathyroid or other neck surgery. This is because the sensitivity of these techniques for the detection of a parathyroid abnormality is far less than that of the expert parathyroid surgeon in a patient undergoing first-time surgery.

Those patients who are not to undergo surgery require an appropriate follow-up. Their serum calcium level should be monitored every 6 months, and urinary calcium and serum creatinine every year, measurements including a cortical site (the distal radius or, where not available, the hip). The general principles of medical therapy in asymptomatic PHPT patients include proper education on the symptoms of hypercalcaemia and dehydration, maintenance of adequate hydration (the choice of a diuretic, if necessary to lower the serum calcium level, being a difficult issue), a recommendation to increase physical activity, and the avoidance of excessive, as well as
Table 2. Guidelines for surgery in primary hyperparathyroidism (PHPT)\textsuperscript{24}

<table>
<thead>
<tr>
<th>Definite indications</th>
<th>Relative indications</th>
<th>Changing to a recommendation for surgery after initial medical management</th>
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<tr>
<td>Serum calcium &gt; 0.25 mmol/l above the upper limit of normal</td>
<td>Age &lt; 50 years</td>
<td>Hypercalcaemia consistently &gt; 0.25 mmol/l above the upper limit of normal</td>
</tr>
<tr>
<td>Hypercalcaemia, renal insufficiency, nephrolithiasis or nephrocalcinosis</td>
<td>Neuromuscular or psychiatric symptoms</td>
<td>Hypercalcaemia or worsening renal function</td>
</tr>
<tr>
<td>Overt bone disease (osteitis fibrosa cystica)</td>
<td>Peptic ulcer disease, pancreatitis</td>
<td>Nephrolithiasis or nephrocalcinosis</td>
</tr>
<tr>
<td>Reduction of bone mineral density</td>
<td>Hypertension</td>
<td>Significant decline in bone mass</td>
</tr>
<tr>
<td>(Z-score ≤ −2 sd)</td>
<td></td>
<td>Episode of acute PHPT</td>
</tr>
<tr>
<td>Episode of acute primary PHPT</td>
<td></td>
<td>Any significant clinical symptom</td>
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restricted, dietary calcium.\textsuperscript{23} The use of oestrogens is recommended in post-menopausal women. Bisphosphonates have not been evaluated for the long-term control of serum calcium level and bone mass in PHPT patients. It should, however, be borne in mind that their very long bone retention and high potency on osteoclastic inhibition may be responsible for a severe post-operative hungry bone syndrome in patients in whom parathyroid surgery becomes indicated. The indications for changing to a recommendation for surgery are listed in Table 2. This general strategy could be challenged in the near future if very recent data favouring surgery are confirmed.\textsuperscript{24} A long-term follow-up of patients with no first-intention surgery has shown disease progression in 27% of initially asymptomatic patients and in all symptomatic patients, whereas patients who underwent surgery had normalized biochemical values and experienced increased bone mineral density.\textsuperscript{25}

Diabetes mellitus and acromegaly

Both of these conditions are considered to be classical risk factors for osteoporosis despite a poor demonstration of a consistently low BMD and increased fracture risk in these patients. Growth hormone and insulin-like growth factors I and II, as well as several types of IGF-binding protein, have actions on bone cells (mainly osteoblasts) in vitro, but the correlation with indices of bone turnover and bone mass in vivo has not been firmly established, either in experimental animal models or in humans. Osteopenia in acromegaly is related to a co-existent hypogonadism.\textsuperscript{26} On the other hand, a low appendicular bone mass has also been reported in children with growth hormone deficiency, which could affect the achievement of peak bone mass.\textsuperscript{27} Recent studies have suggested that osteopenia can be observed in insulin-dependent (type I) but not in type 2 diabetes mellitus.\textsuperscript{28–30} Research is clearly needed to establish the patterns of bone involvement in both types of diabetes, the incidence of fractures and the therapeutic consequences in diabetic patients. It should be recalled that acromegalic patients have an increased risk of developing colonic tumours, which may be diagnosed as a result of vertebral bone metastasis.
**Practice points**

- Osteopenia is a clinical feature of several endocrine disorders. This paradigm has two practical consequences: first, any excess of thyroid, parathyroid or glucocorticoid (GC) hormones should be assessed in pre-menopausal women and in men with a low bone mass or osteoporotic fractures; and second, bone mineral density should be measured in any patient with these endocrine disorders.

- Bone involvement occurring during endocrine disorders may deserve a specific therapeutic intervention: anti-osteoclastic agents such as bisphosphonates should be considered in patients with severe osteoporosis.

- An endocrine disorder is discovered in about 25–30% of male patients with osteoporosis.

- The complex interaction of hypogonadism and nutritional disorders may impair the achievement of optimal peak bone mass and/or induce severe pre-menopausal bone loss in young females with anorexia nervosa or in overtrained athletes.

- GC-induced osteoporosis is the most frequent cause of secondary osteoporosis.

- Most of the loss of bone induced by systemic GC therapy occurs within the first year; bone densitometry screening and prevention are therefore required early.

- An exposure to high doses (endogenous or exogenous) of thyroid hormones is associated with bone loss, especially in post-menopausal women.

- Primary hyperparathyroidism (PHPT) may be diagnosed in an asymptomatic normocalcaemic patient presenting with osteopenia or osteoporosis.

- Parathyroid surgery has a very high success rate in PHPT, but medical management may be recommended in some selected patients.

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**Research agenda**

- Therapeutic trials are needed to explore the long-term risk/benefit ratio of hormone replacement therapy or anti-osteoclastic (such as bisphosphonates) or anabolic agents in hypogonadal females or males, in order to improve the management of patients with early severe osteoporosis.

- A longitudinal follow-up of large cohorts of GC-treated patients will allow researchers to explore the variability and reversibility of GC-induced osteoporosis.

- Controlled observational studies and therapeutic trials in patients treated with thyroid hormones will improve the understanding of thyroid hormone action on bone, as well as clinical management.

- The potential of calcimimetic agents (activating the calcium-sensing receptor of parathyroid cells) in PHPT must be explored.

- The anabolic potential of PTH on bone in idiopathic osteoporosis needs to be investigated.

- Longitudinal studies of diabetes mellitus patient cohorts will allow the observation of bone status and define optimal clinical management.
EXTRA-OSSEOUS DISORDERS OF ENDOCRINE ORIGIN

Hypogonadism

No joint disease has been associated with primary hypogonadism. Young women with secondary amenorrhoea related to anorexia nervosa can present with an unexpected tophaceous gouty arthritis secondary to the long-term use of diuretics. The electrolyte profile is characteristic, with renal failure, hypokalaemia and the detection of diuretics (furosemide and thiazides) in the urine. Prevalence and outcome are unknown since information on this secondary gout is only based on case reports.

Hypercorticism

Iatrogenic hypercorticism is more likely than Cushing’s syndrome to produce musculoskeletal side-effects, in terms of both prevalence and severity. Musculoskeletal involvement can, however, be the presenting feature at the time of diagnosis or can appear during the course of the diseases.

Muscles

Steroid-induced myopathy is significantly associated with GC-induced osteoporosis but remains unapparent until other signs of GC excess are present. A delay in onset is variable and may be short. The condition is usually a consequence of high-dose steroid therapy, fluorinated steroids being associated with a higher risk. Specific bone involvement caused by steroid inhalation has been reviewed in two meta-analyses, but there are no available data on the muscular consequences. The bone and muscle side-effects of oral budesonide, a topical steroid used in Crohn’s disease, are currently unknown. The nutritional and cardiorespiratory aspects of steroid-induced myopathy should be investigated.

The painless myopathy associated with excess adrenocorticotropic hormone (ACTH) and steroid treatment has a relatively non-specific pattern of proximal muscle weakness affecting the thighs more than the arms. Ventilatory muscle weakness can be present, with an elevated diaphragmatic pattern. Amyotrophy of the proximal muscles is frequent. An elevated serum muscle enzyme concentration is uncommon but increased urine creatinine excretion is a classical feature. The atrophy produced by endocrine disorders, including excess GC and thyroid hormones, is primarily the result of alterations in carbohydrate, protein and electrolyte metabolism. Type II muscle fibres are therefore more severely affected than type I fibres. Muscle biopsy, usually performed on the quadriceps, characteristically demonstrates an increased variation in the diameter of muscle fibres, as well as diffuse necrotic and basophilic fibres.

The treatment of steroid myopathy has not been fully evaluated. Current recommendations include a reduction of the steroid dose, along with the use of topical steroids including steroid inhalations in lung disease and the new topically active oral GC budesonide in Crohn’s disease, the avoidance of fluorinated GCs when possible, and exercise or physical therapy. A few studies in heart transplant patients have evaluated the preventative effect of resistance exercise on muscle involvement and recovery, with promising results. The outcome is usually good, with long-term recovery following a decrease in the steroid dose, but the prognostic and preventative factors deserve further study.
Tendinopathy

Iatrogenic hypercorticism can lead to tendinitis and tendon rupture in patients on long-term and high-dose steroid therapy. Additional risk factors include local steroid injections, terminal renal failure and fluoroquinolone antibiotics. Achille's tendon rupture is the archetype of this complication and can mimic calf phlebitis. Thompson's sign is pathognomonic: in a normal subject lying prone, pressure on the calf leads to a plantar flexion of the foot, but when tendon rupture occurs, the test does not provoke any flexion of the foot. Management is currently a matter of controversy, oscillating between surgical repair and orthopaedic management.39

Septic arthritis and pyomyositis

Septic arthritis has not been reported as a feature of Cushing's syndrome in spite of a high circulating level of cortisol; in contrast, GC-induced hypercorticism is a major risk factor for septic arthritis and pyomyositis.

Avascular osteonecrosis and secondary osteoarthritis

Cushing's disease and mainly GC therapy are major causes of usually multiple and bilateral avascular osteonecrosis (AVN). In decreasing order of frequency, the femoral heads, the humeral heads, the femoral condyles, the tibial plateaux and the talus can be involved, even simultaneously. AVN can be localized to the epiphyses or can spread to the metaphyses, giving a specific pattern of bone infarcts. GC-induced osteoporosis is frequently also seen. The pathophysiology of AVN has not yet been ascertained.

Management is palliative, although complete regression of the MRI abnormalities has been observed in renal transplant patients on imaging follow-up. The injection of acrylic cement into the femoral head has been proposed as an alternative to core decompression40,41, but further study is needed. Total joint replacement may be required.

Epidural lipomatosis

A non-encapsulated accumulation of fat in the spinal canal may represent a complication of Cushing's syndrome, obesity or hypothyroidism, or less rarely be a consequence of corticosteroid therapy. Idiopathic epidural lipomatosis is a rare condition (see the review by Benamou et al42). The prevalence of iatrogenic epidural lipomatosis has probably been underestimated since only symptomatic cases have been reported in the literature and no systematic imaging study has been performed.

This disorder usually follows the chronic administration of GCS at a moderate-to-high dosage, as in heart and kidney transplant recipients and asthmatics, or even at a lower dosage in systemic diseases including polymyositis and rheumatoid arthritis. A dose of prednisone above 20 mg per day for at least 6 months or under 20 mg per day for at least 5 years' duration is a risk factor. A shorter treatment duration with a higher dose and multiple epidural steroid injections have also been reported to cause epidural lipomatosis.

Symptoms depend upon the site and diffusion of epidural lipomatosis. The usual deposition site is the thoracic spine between T4 and T10, the L4–L5 level being more rarely involved. Symptoms include thoracic and/or lumbar back pain, sciatica, paraparesis and cauda equina compression with bladder dysfunction. Lower limb
weakness can be a presenting feature and lead to difficulties of diagnosis in the clinical setting of polymyositis or steroid-induced myopathy. Medullary symptoms, including a positive Babinski sign, brisk reflexes and sphincter dysfunction, should be recognized as diagnostic signs.

Investigations include standard radiographs, CT scanning and MRI. Plain X-rays can disclose vertebral crush fractures. Depending on the techniques available, CT scans and MRI studies are considered to be the best diagnostic procedures for demonstrating dural compression by an adipose mass, with specific densities on CT scanning and on MRI in T1-weighed images. Sagittal MRI scanning allows one to demonstrate the extent of the epidural lipomatosis; myelography is less often used. Disc herniation and vertebral fractures may be associated, worsening the condition.

The pathogenesis of epidural lipomatosis is unknown. Its usual location in the thoracic spine is probably caused by the presence of a larger amount of fat tissue at this site. Additional factors, including lipid metabolism abnormalities and diabetes mellitus, may play a part and should be sought. Further studies are needed to assess the role of GC bio-availability, GC-induced hyperinsulinism and GC receptor distribution and mutation.43 Management should take into account the severity and duration of the symptoms, the nature of underlying disease and the possibility of its control while tapering the steroid dosage. When facing sudden-onset and severe neurological involvement, treatment has usually relied primarily on surgery, laminectomy over the length of the dural compression and removal of the fatty tissue.44 Infectious complications of surgery have been reported. In mild cases, a reduction of steroid dosage and nutritional management can improve the neurological symptoms, with a longer recovery period. Repeated imaging (CT scanning or MRI) studies have shown a regression of lipomatosis in isolated cases. Time necessary for recovery is unknown and could be addressed by prospective studies. A reduction of body weight may be effective when the affected patient is obese.

Acromegaly

Human growth hormone (hGH) overproduction, usually as a result of a pituitary tumour, leads to significant effects on the soft tissues, bones and joints. The overproduction of hGH stimulates the production of insulin-like growth factor-1 by the liver. Both hormones have direct and indirect effects on bone and cartilage cells, resulting in articular and peri-articular soft tissue hypertrophy and bone overgrowth. Besides bone involvement, musculoskeletal complaints are frequent in patients with acromegaly and may impair their quality of life even after the cure of their pituitary adenoma. Dons et al have proposed a pragmatic classification for articular disease severity according to medical management.45

Characteristics changes in the face and enlargement of the extremities are associated with headache, visual disturbance and skin changes, including hirsutism and excessive sweating. Besides the dysmorphic syndrome, acromegalic patients frequently present with rheumatological complaints, which affect 10–17% of patients at the time of onset45 and 50–70% of patients with clearly identified disease.45,46 However, these figures include symptoms not directly related to hGH hypersecretion, such as degenerative changes or unrelated symptoms. As shown in Table 3, rheumatological complaints are associated with peripheral and spinal involvement, as well as with soft tissue abnormalities. True acromegalic arthropathy starts 5–10 years after the onset of the endocrine disease, with a relationship to hGH level at base-line. In addition, as suggested in a retrospective study, this delay decreases with patient age.49
<table>
<thead>
<tr>
<th>Table 3. Musculoskeletal disorders in acromegaly.</th>
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<tbody>
<tr>
<td>Peripheral joint involvement</td>
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<tr>
<td>- arthralgia</td>
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<tr>
<td>- acromegalic arthropathy (with or without symptoms)</td>
</tr>
<tr>
<td>Spinal involvement</td>
</tr>
<tr>
<td>- cervical, thoracic and lumbar pain</td>
</tr>
<tr>
<td>- vertebral crush fractures (metastasis, hypogonadism, hyperprolactinaemia and hyperparathyroidism are to be discussed)</td>
</tr>
<tr>
<td>- association with diffuse idiopathic vertebral hyperostosis</td>
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<tr>
<td>Neurological involvement</td>
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<tr>
<td>- carpal tunnel syndrome</td>
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<tr>
<td>- myalgia</td>
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<tr>
<td>- nerve root compression from spinal origin (including cervical, sciatic and crural nerve root compression, spinal stenosis and myelopathy)</td>
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<tr>
<td>- myopathy</td>
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<tr>
<td>Raynaud’s phenomenon?</td>
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**Arthralgias, myalgias and carpal tunnel syndrome**

Arthralgias and myalgias, usually associated with carpal tunnel syndrome, are frequent and resolve after treatment of the pituitary adenoma. The clinician should focus his or her attention on unusual constitutional symptoms and slight dysmorphic signs (glove and shoe size changes, a comparison of past and recent pictures of the patient’s face, sweating and asthenia). Isolated cases of seronegative polyarthritis resolving after cure of the pituitary adenoma have also been reported.  

**Acromegalic limb arthropathy**

According to three retrospective studies, acromegalic limb arthropathy is most common in the large joints (knees, shoulders and hips, in decreasing order of frequency). Mechanical-type pain is usual, but inflammatory arthralgias are not uncommon, especially in the hands and shoulders. In early disease, the range of motion is normal or may even be increased. Crepitus is considered to be frequent. In late disease, increased pain and limitation of joint motion appear as a consequence of secondary osteoarthrosis. Joint effusions are observed in 5% of patients and should be tested for calcium pyrophosphate dihydrate (CPPD) crystals. Radiologically, characteristic or even pathognomonic changes are described: soft tissue and cartilage hypertrophy, periosteal new bone formation, and the production of marginal and subligamental new bone. Ultimately, cartilage degeneration occurs, resulting in destructive osteoarthrosis. Articular mobility is also impaired by the prolific osteophytes. The differential diagnosis between primary and acromegalic osteoarthrosis may be difficult. Epiphyseal (square-shaped) deformation and large osteophytes are two pointers in the radiological diagnosis of acromegaly.

Questions remain regarding first the delay of onset of such degenerative changes after cartilage hypertrophy, and second, the possibility of symptom relief and cartilage recovery after cure of the hypophyseal adenoma.

No definite data are available on the morphological outcome in peripheral acromegalic arthropathy in terms of progression with or without treatment. There are anecdotal reports showing the sequence of events from cartilage hypertrophy to
narrowing and destructive changes (Figures 1–4). One retrospective study has suggested that arthropathy can progress independently of a fall in hGH level once significant cartilage overgrowth has developed.\textsuperscript{45} Conversely, two other clinical retrospective studies have shown that conventional (radiotherapy or surgery) treatment of the adenoma does improve the symptoms of acromegalic arthropathy.\textsuperscript{47,48} A better understanding of outcome is needed, especially for the larger joints such as the shoulders and the knees.

Only one prospective study\textsuperscript{50} has evaluated the structural effect on cartilage of 6 months' treatment with subcutaneous injections of octreotide (OCT), an hGH-suppressing drug, measuring the thickness of articular cartilage in the shoulder, wrist and knee in 30 acromegalic patients compared with 18 healthy subjects.\textsuperscript{50} Using
ultrasonography, this study demonstrated three striking results. First, a significant increase in the thickness of wrist and knee cartilage was found in patients with active disease compared with those with inactive disease. Second, a significant decrease in the thickness of cartilage in the shoulder, wrist and left knee was found after 6 months of OCT treatment. Third, no difference in heel tendon size was observed between normal subjects and acromegalic patients whose disease had been inactive for 2 years, suggesting that with sustained control of the hGH level, a partial-to-complete recovery might be possible at specific articular ad peri-articular sites. This single study is encouraging but deserves further evaluation to confirm these observations, the precision of cartilage thickness measurement by ultrasound, and its inter- and intra-observer variations.
Spinal involvement

In acromegaly, spinal involvement is classically described with kyphosis, chronic dorsal and lumbar pain, nerve root compression at cervical and lumbar sites, and spinal stenosis syndrome. Radiographic abnormalities have been fully described, including new bone formation on the anterior surfaces of vertebrae (Erdheim's spondylosis) and subsequent anteroposterior enlargement, ligamentous calcification, increased intervertebral disc spaces, and scalloping of the posterior margins, especially in the lumbar spine. These features are also frequently associated with degenerative spinal processes and with diffuse idiopathic skeletal hyperostosis (DISH). Consequently, all the symptoms are not specifically related to acromegalic changes. It should be recalled that even if several radiological features are shared by DISH and acromegaly patients, the level of GH and non-suppressible insulin-like activity, including that of somatomedin, has been found to be similar in patients with DISH and controls. Uncommon inflammatory-type spinal pain has been reported in acromegalic patients without specific radiological or bone scan abnormalities. MRI studies might provide an explanation for such clinical patterns.

Raynaud's phenomenon

Raynaud's phenomenon has been reported in up to 25% of acromegalic patients, but this association is debated. A thickening of the small vessel wall would contribute to distal limb vasculopathy. Nailfold capillaroscopy studies suggest that the microcirculation is altered in acromegalic patients with active disease compared with those with inactive disease.

Management

Endocrinologists and patients clearly state that after surgical removal of their pituitary adenoma, the generalized aching, including arthralgias, myalgias and carpal tunnel syndrome, frequently resolves within weeks. Improvement is slower after pituitary irradiation, which is usually given as a second- or third-line therapy when surgery is not sufficient to normalize the hGH level. Two somatostatin analogues are currently available: octreotide and lanreotide. Octreotide is given by daily (Sandostatine) subcutaneous injection or as a long-acting, slow-release formulation (Sandostatine LAR), every 28 days. Lanreotide (Somatuline PR) is administered every 10 days. These molecules act directly on the pituitary adenoma by suppressing GH secretion. The choice of agent depends upon the effectiveness and the tolerability of the drug, better patient comfort being achieved with long-acting compounds. However, a recurrence of side-effects (abdominal discomfort and steatorrhoea) has been reported after lanreotide injection. In future, a GH antagonist employing modifications to the natural hormone will be able to act at the GH target level by antagonizing the hormone's effect. So far, however, there are no published data on the effect of this molecule at the articular level.

The symptoms of acromegalic limb arthropathy are inconsistently improved by suppressing hGH hypersecretion by means of successful pituitary surgery. Analgesics, non-steroidal anti-inflammatory drugs and/or intra-articular joint injections are currently used for refractory symptoms, although not all have been evaluated by prospective trials. GH analogues have a specific analgesic effect independent of the
control of GH level.\textsuperscript{55,56} Headache related to pituitary adenoma resolves within minutes of GH analogue injection before any reduction in hGH level.\textsuperscript{56}

Destructive arthropathies of the hip, knee and shoulder can benefit from total arthroplasty as has been mentioned in single case reports or short series.\textsuperscript{57} The outcome appears to be favourable in the small number of cases described. Larger studies are needed, especially of the shoulder joint. Osteotomy has also been proposed in patients with secondary osteoarthritis, but the long-term outcome is currently unknown.

**Diabetes mellitus**

The late complications of diabetes mellitus are related to the two salvage (aldolase reductase and non-enzymatic glycation) pathways stimulated by chronic hyperglycaemia. An abnormal activation of the sorbitol pathway is the main cause underlying the development of diabetic neuropathy. Sorbitol also accumulates in excess in nervous tissues and causes damage by an osmotic mechanism. Both hyperglycaemia and the activation of aldolase reductase result in the overproduction of free oxygen radicals and in nitric oxide downregulation. More importantly, activation of the sorbitol pathway leads to non-enzymatic protein glycation, which results in the accumulation of irreversible advanced glycation products (AGEs) able to generate reactive oxygen intermediates and to interact with specific cellular receptors.\textsuperscript{58} The presence of AGEs has been linked to the onset and progression of vasculopathy in diabetes. AGE-modified long-life proteins in the extracellular matrix alter the basement membranes by increasing vascular permeability and trapping plasma macromolecules.\textsuperscript{59} The non-enzymatic glycation of collagen IV leads to an increased number of cross-links that resist collagenases, reduce collagen turnover, increase vessel wall rigidity and lead to collagen accumulation in the soft tissues. As a result, increased vascular resistance induces a decrease in tissue perfusion, leading to nerve hypoxaemia. Thus, the articular and neurological complications of diabetes mellitus are thought to be related to both vasculopathy and neuropathy on the one hand\textsuperscript{60}, and the abnormal accumulation of proteins in soft tissues on the other.

In this chapter, only specific rheumatological disorders will be reviewed Table 4. A recent review by Vinik provides a large amount of information on diabetic neuropathy\textsuperscript{60}, neuroarthropathies also being reviewed in this volume.

**Connective tissue disorders**

Several connective tissue disorders (CTDs) are directly related to diabetes mellitus as a result of abnormal collagen modulation.\textsuperscript{61}

*Dupuytren's disease.* Dupuytren's disease (DD) is a spontaneously occurring chronic and idiopathic thickening of the palmar aponeurosis leading to various degrees of flexion deformity of the metacarpophalangeal and proximal interphalangeal joints of the fingers. The plantar aponeurosis and other tissues (as in Lapeyronie's disease and thickening of the knuckle pads) can be involved to a lesser frequency and degree.

The aetiology of this condition is unknown but several factors have been associated with DD, including genetic predisposition, epilepsy and alcohol abuse. The reported prevalence of DD in diabetic patients is clearly increased, varying from 2% to 65% depending on the patient's age and ethnic origin.\textsuperscript{61} The precise reasons for such a high prevalence are currently unknown. It has been postulated that neuropathy,
Table 4. Musculoskeletal manifestations in diabetes mellitus.51

<table>
<thead>
<tr>
<th>Secondary to neurological dysfunction</th>
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<tbody>
<tr>
<td>– diabetic neuropathy</td>
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<tr>
<td>– mononeuritis</td>
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<td>– muscular ischaemia</td>
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<tr>
<th>Secondary to infection</th>
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<tbody>
<tr>
<td>– diabetic neuroarthropathy</td>
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<tr>
<td>– osteitis/osteomyelitis</td>
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<tr>
<td>– septic arthritis (Staphylococcus aureus)</td>
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<td>– pyomyositis (Staphylococcus aureus)</td>
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<table>
<thead>
<tr>
<th>Secondary to collagen involvement</th>
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<tbody>
<tr>
<td>– Dupuytren’s contracture</td>
</tr>
<tr>
<td>– shoulder capsulitis</td>
</tr>
<tr>
<td>– diabetic cheiroarthropathy</td>
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<tr>
<td>– trigger finger</td>
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</table>

Microvascular changes and control of the metabolic disease could influence the rate of DD. Recent cross-sectional studies have, however, shown that DD is significantly associated with patient age and the duration of the diabetes, but not with the age of onset, the control of the diabetes or the body mass index.62–65 The prevalence of DD has been found to be similar in type I and II diabetic subjects but type I subjects were younger, as expected in this study.66 In cross-sectional studies, DD was also associated with visceral involvement resulting from the diabetes, including symmetrical polyneuropathy, as well as a history of myocardial infarction, conditions that could be related to the age of the patients. Cheiroarthropathy, in which no nodule or cord is noticed on palpation, can be associated with DD. Pryer’s sign and the table sign are positive in both conditions. Trigger finger also frequently occurs with both conditions, but nodular flexor tendon enlargement is quite different from DD’s nodule.

Only one follow-up study of diabetes from Finland clearly showed that DD occurred at a rate of 2% of new cases per year during the 5 years of the study.65 Overall, the age of the patient and the duration of the diabetes were associated with DD. Again, time-related variables explained the apparent previous association with retinopathy, neuropathy and nephropathy or hypertension.

Current management includes both surgery and non-surgical procedures. Indications for treatment depend upon the severity of the flexion contractures and the resulting instability. According to Tubiana’s classification, as soon as the patient has experienced a positive table sign, treatment should be considered. Under regional or general anaesthesia, the surgical procedure includes incision, digital Z-plasty if needed, subtotal fasciectomy and physiotherapy several days post-operatively.

Percutaneous needle fasciectomy was proposed by Debeyre in Paris in 195867 and modified by Lermusiaux. This simple and reliable technique is performed on an outpatient basis, with local anaesthesia around the palmar nodule. Sections of the nodule and the cord is obtained by moving the needle up and down; the finger is then passively extended by the operator, resulting in a cracking of the cord and extension of the finger. A splint can be prepared in order to maintain the finger in position for a few days. Complications are rare with a trained operator and are usually benign, without tendon or vascular bundle lesions.
To date, no controlled study comparing surgical and closed needle procedures has been performed. Open series have shown an excellent or good outcome in 81% of cases in the short term and 50–69% at 5 years. The recurrence rate is 50% at 5 years. Two procedures can be performed in conjunction with one another, the needle fasciotomy being performed as a preliminary procedure. A comparison between idiopathic and diabetes mellitus-associated DD is awaited. Surgical treatment of a trigger finger can be performed during the same procedure.

Shoulder capsulitis. ‘Frozen shoulder’, or shoulder capsulitis, is a common complication of diabetes mellitus, the prevalence ranging from 10.3% to 31.8% in diabetic patients, with an increased frequency in type II (non-insulin-dependent) diabetes. Bilateral shoulder capsulitis is more common in diabetics than in control subjects. Diabetic shoulder capsulitis seems to appear at a young age, may be indolent or less painful, and may last longer than non-diabetic shoulder capsulitis.

Its management is based on analgesics, local injection of steroids under close monitoring of the blood sugar level, rehabilitation and auto-exercise procedures, although controlled studies of treatment are needed.

Pyomyositis and septic arthritis. As observed in patients treated with long-term steroid therapy, those with diabetes mellitus, especially when their disease is out of control, are at risk of developing septic arthritis and pyomyositis. Specific host defences such as phagocyte function are impaired in diabetes mellitus, thus predisposing to infectious complications. As a consequence, the risk of septic arthritis in a patient with diabetes mellitus has been estimated at 3.3 in a prospective study comparing risk factors in patients with joint diseases attending a rheumatic disease clinic for 3 years. Staphylococcus aureus is the micro-organism most commonly responsible for joint infections in these patients. Differential diagnosis includes diabetes muscle infarction.

Parathyroid disorders

Hyperparathyroidism

Besides bone resorption, primary and secondary hyperparathyroidism can cause articular and peri-articular disorders. Patients may present with generalized muscular aching and stiffness, pain and tenderness at sites of tendon insertion and, as an unusual feature, joint laxity and spontaneous tendon rupture. Pseudo-clubbing of the fingers is possible in children and more rarely in adults. Subchondral bone resorption can lead to an erosive arthropathy of the small joints of the fingers and wrists involving the peri-articular and articular sites, along with CPPD crystal deposition disease. Interestingly, an increase in serum PTH 44–68 level has been observed in patients with genetic haemochromatosis associated with osteoarticular changes.

The association between PHPT and CPPD crystal deposition disease is well recognized. The radiographic changes of CPPD crystal deposition have been reported in up to 40% of patients with hyperparathyroidism. Chondrocalcinosis is age related. Parathyroidectomy does not cause regression of the chondrocalcinosis or symptomatic improvement, and may be followed by acute attacks of pseudo-gout. The preventative management is still debated but can be achieved with oral calcium supplementation and/or colchicine administered before surgery. Controlled studies are not available.
Thyroid disorders

Hypothyroidism

Muscle disease. Muscular involvement is classically associated with hypothyroidism, including in some cases muscle pain, cramps, muscle weakness and calf muscle hypertrophy. The muscle symptoms can be isolated or can be associated with a slightly elevated serum creatinine phosphokinase (CPK) concentration that may reveal thyroid hormone insufficiency. The differential diagnoses include polymyalgia rheumatica, fibromyalgia, drug-induced muscular disorders and polymyositis. Unusual muscular presentations include polymyositis-like disorder, respiratory muscle weakness, muscle stiffness and pseudohypertrophy (Hoffmann’s syndrome), and periodic hypokalaemic paralysis.

Chondrocalcinosis and gout. The association between hypothyroidism and CPPD has been suggested in single cases or short series. Recent case control studies have ruled out this association, although a recent meta-analysis by Jones et al suggested a consistent trend for a weak association between these diseases.

Hyperuricaemia was believed to be associated with hypothyroidism. Some controversy, however, arises. Conversely, the prevalence of hypothyroidism was found to be increased in both patients with crystal-proven gouty arthritis in a prospective study and those receiving uric acid-lowering medication in a retrospective survey. Its prevalence was higher in female than in male patients in both prospective (25% and 12% respectively) and retrospective (40% and 15% respectively) studies. The hyperuricaemia may result from reduced uric acid clearance, which can be increased by hormone supplementation.

Thyroiditis and other autoimmune conditions. Systemic lupus erythematosus and Sjögren’s syndrome are the two most frequent autoimmune diseases associated with thyroiditis. Half of all patients will have the two diagnoses made at the same time. Sjögren’s syndrome and autoimmune thyroiditis appear to be closely related pathogenetically since immunopathological features of sialadenitis similar to those diagnostic of Sjögren’s syndrome have been found in labial salivary gland biopsies from patients with autoimmune thyroid disease.

Rheumatoid arthritis has been classically associated with thyroiditis but few controlled studies are currently available. A higher prevalence, albeit not always reaching statistical significance, of thyroid dysfunction, as defined by a low TSH level or the presence of anti-thyroid antibodies, has been observed in rheumatoid arthritis patients than normal controls or those with non-inflammatory rheumatological conditions. The prevalence of thyroid abnormalities ranged from 22.8% to 30% in rheumatoid arthritis patients. In Shiroky’s study, thyroid dysfunction, including hypothyroidism and Hashimoto’s thyroiditis, was seen at least three times more often in women with rheumatoid arthritis than women with non-inflammatory conditions such as osteoarthritis and fibromyalgia. However, seronegative oligoarthritis or polyarthritis may occur in the setting of thyroiditis, as suggested by Punzi et al in a cohort study of 33 patients with thyroiditis and arthritis. These non-rheumatoid polyarthritis and oligoarthritis patients were characterized by frequent spontaneous remission, the absence of bone erosions, a low synovial fluid level of interleukin-1β and an increased titre of HLA-DR3.
Thyrotoxicosis

Myopathy. Contrasting with polyphagia and polydipsia, adipose and muscular tissues are severely affected by thyroid hormones produced in excess. As a consequence, weight loss is associated with proximal muscle wasting and respiratory muscle weakness. Non-specific related symptoms include asthenia, fatigue, an inability to rise from one's seat and dyspnoea. The classical clinical features of Graves’s disease—thyroid gland enlargement and ocular signs—give clues to diagnosis that are confirmed by measuring TSH and free T4 hormone levels. The serum CPK level is usually within the normal range. Electromyographic studies disclose a myopathic pattern without specific features. Myopathy regression is achieved with anti-thyroid therapy.

Practice points

Acromegaly

- mild characteristic changes (acral, face, intra-abdominal and thoracic organ enlargement) are usually present when non-specific arthralgias, myalgias and carpal tunnel syndrome associated with excessive perspiration, headache, diabetes and hypertension are the presenting features
- a comparison of photographs and glove and shoe sizes is useful for diagnosis
- cartilage hypertrophy and exuberant osteophyte formation are the initial radiological hallmarks of acromegalic arthropathy

Endocrine myopathy

- proximal muscle weakness, without nerve root abnormalities, should lead to the search for an endocrine myopathy
- the serum CPK level is usually normal or slightly elevated
- electromyographic studies are usually normal or show a mild myopathic pattern

Hypothyroidism

- hypothyroidism should be considered in the setting of muscle cramps or pain, a slightly elevated serum CPK concentration and usually normal electromyographic studies
- measurement of the serum TSH level is useful for diagnosis
- an isolated high serum CPK concentration should provoke the measurement of TSH level since hypothyroidism is frequently associated

GC-induced myopathy

- patients with GC-induced myopathy present with painless proximal muscle weakness and normal serum CPK level and electromyographic studies
- the disorder usually follows high-dose steroid therapy

Hyperparathyroidism

- radiological findings of chondrocalcinosis, with the exception of isolated meniscalcalcinosis in the elderly, should lead the clinician to check the serum calcium level

Diabetes mellitus

- blood sugar level should be checked in patients with DD, especially women
Research agenda

acromegaly
- mechanisms of pain in acromegalic arthropathy
- association with CPPD disease
- association with Raynaud's phenomenon
- joint outcome after control of the hypersecretion of growth hormone, including
  prognostic factors with respect to improvement or the onset of secondary
  osteoarthritis
- cartilage thickness changes by X-rays, MRI studies and ultrasonography
- outcome of surgical management of large joint acromegalic arthropathies
  (e.g. hip, knee and shoulder)
- analgesic effects of somatostatin analogues

hypercorticism
- predictive and prognostic criteria for steroid-induced myopathy
- treatment and prevention of steroid-induced myopathy with respect to exercise
  training programmes
- alternative treatment for AVN of bone: acrylic cement injection or bone
  morphogenic protein core injection

hypothyroidism
- relationship between rheumatoid arthritis and thyroiditis to be further
  investigated by genetic studies

diabetes mellitus
- prevalence of CTDs in other forms of diabetes mellitus such as maturity-onset
  diabetes of the young and in patients' relatives
- prognostic factors (autonomic neuropathy, polyneuritis and others) and the
  early prevention of neuropathic arthropathies
- relationship between trigger finger and cheiroarthropathy
- pathophysiology of DD in diabetes mellitus
- conservative treatment by local steroid injection and dissection in DD in
  diabetics
- comparison between surgical procedures and closed needle fasciotomy in DD

Unusual thyrotoxic muscle presentations include rhabdomyolysis and myositis-like
features including an elevated serum CPK level without muscle necrosis. In some
Asiatic patients, a periodic paralysis may be associated with thyrotoxicosis.

Achropacy. This rare condition is characterized by soft tissue swelling of the hands and
feet with clubbing and periosteal new bone formation. In 1968, Kinsella and Beck
reported 317 cases in the literature.\textsuperscript{90} The classical description includes exophthalmos
and pretibial myxoedema. Radiographs disclose fluffy subperiosteal bone formation
and soft tissue swelling. This diaphyseal bone formation is best noticed on the radial
aspects of second and third metacarpals. Achropacy occurs in patients with treated
thyrotoxicosis, sometimes with a long interval between the onset of the two conditions. No treatment is currently available, and the symptoms diminish over years whether or not thyroid function is corrected.

REFERENCES


34. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy. A systematic review and meta-analysis. Archives of Internal Medicine 1999; 159: 941–955.


Disorders of endocrine origin


