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REVIEW

# Extrathyroidal manifestations of Graves' disease: a 2014 update

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**Abstract**
*Introduction* Graves' orbitopathy (GO), thyroid dermopathy (also called pretibial myxedema) and acropachy are the extrathyroidal manifestations of Graves' disease. They occur in 25, 1.5, and 0.3 % of Graves' patients, respectively. Thus, GO is the main and most common extrathyroidal manifestation. Dermopathy is usually present if the patient is also affected with GO. The very rare acropachy occurs only in patients who also have dermopathy. GO and dermopathy have an autoimmune origin and are probably triggered by autoimmunity to the TSH receptor and, likely, the IGF-1 receptor. Both GO and dermopathy may be mild to severe.
*Management* Mild GO usually does not require any treatment except for local measures and preventive actions (especially refraining from smoking). Currently, moderate-to-severe and active GO is best treated by systemic glucocorticoids, but response to treatment is not optimal in many instances, and retreatments and use of other modalities (glucocorticoids, orbital radiotherapy, cyclosporine) and, in the end, rehabilitative surgery are often needed. Dermopathy is usually managed by local glucocorticoid treatment. No specific treatment is available for acropachy.
*Perspectives* Novel treatments are presently being investigated for GO, and particular attention is paid to the use of rituximab. It is unknown whether novel treatments for GO might be useful for the other extrathyroidal manifestations. Future novel therapies shown to be beneficial for GO in randomized studies may be empirically used for dermopathy and acropachy.

**Keywords** Graves' disease · Graves' orbitopathy · Thyroid dermopathy · Thyroid acropachy · Glucocorticoids · Biologics · Rituximab

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## Introduction

Graves' disease is the most common cause of hyperthyroidism in iodine sufficient geographical areas [1] with an incidence of 21 cases per 100,000 per year [2]. In addition to signs and symptoms of hyperthyroidism that are shared with other causes of thyrotoxicosis, Graves' disease is specifically characterized by extrathyroidal manifestations, including Graves' orbitopathy (GO) [3], thyroid dermopathy (or pretibial myxedema) (PTM) and thyroid acropachy [4]. These manifestations are rare except for GO. Orbital disease is detectable on clinical grounds in approximately 25 % of Graves' patients at diagnosis and is most commonly mild. Moderate-to-severe forms account for 5 % of cases, and very rarely progresses to sight-threatening forms [5, 6]. PTM occurs in 4 % of patients with GO [7] and in 13 % of those with severe GO [8]. It can be assumed that PTM may be present in approximately 1.5 % of Graves' patients seen in non-tertiary referral centers (Fig. 1). Almost all patients with thyroid dermopathy have significant GO, but exceptional cases of patients with PTM as presenting manifestation of Graves' disease have been described [9]. PTM in 20 % of cases is associated with thyroid acropachy, mostly in the form of digital clubbing and, in more advances cases,

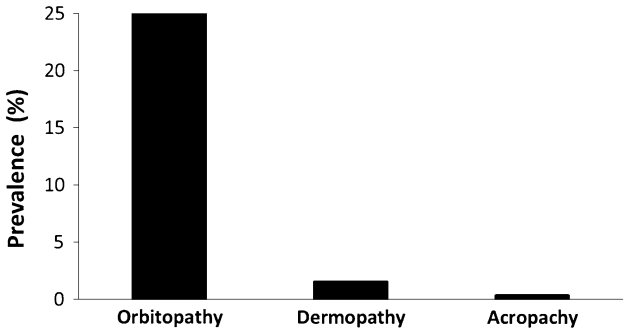


**Fig. 1** Prevalence of Graves' orbitopathy, thyroid dermopathy and acropachy in patients with Graves' disease. Estimates are derived from refs. [4] and [5]

with periosteal reaction of distal bones [10]. Prevalence of thyroid acropachy in Graves' disease can be calculated to be around 0.3 % (Fig. 1). More than 90 % of patients with extrathyroidal manifestations have a history of hyperthyroidism, but a minority have euthyroid Graves' disease or are hypothyroid [3, 4, 11].

## Graves' orbitopathy

### Histopathologic findings and pathogenesis

Most of the clinical signs and symptoms of GO can be explained by the increased volume of the orbital content. This is due to proliferation of orbital fibroblasts, expansion of fat tissue due to differentiation of preadipocyte fibroblasts into adipocytes, enlargement of extraocular muscles due to infiltration by inflammatory cells and increased glycosaminoglycans [12, 13]. Histopathologically, expansion of fibroadipose tissue may represent the main histopathological change in some patients, whereas enlargement of extraocular muscles may prevail in other patients. Increased production of glycosaminoglycans by fibroblasts is an important feature, because these substances are hydrophilic and attract water, thus contributing to intraorbital edema and congestion [12, 13]. In advanced stages of the disease, fibrotic changes may occur in the affected muscles. Owing to space constraint, the increased orbital content may cause compression of the optic nerve (dysthyroid optic neuropathy, DON), particularly at the orbital apex [3].

GO is an autoimmune disorder. Numerous studies have insofar failed to define the basis of genetic predisposition to develop the disease [12]. The link of GO with the thyroid resides with the existence of one or more antigens shared by the thyroid and the orbital tissues [14]. According to the "shared antigen" hypothesis, autoreactive T-lymphocytes reach the orbit and recognize the shared antigen(s) presented by macrophages and B cells: this triggers a series of reactions, including secretion of a number of cytokines which contribute to perpetuate reactions in the orbital space and the related changes described above [12, 13]. Because of the established role of TSH receptor antibodies (TRAb) as ultimate factor responsible for Graves' hyperthyroidism and with consideration that TSH receptors have been demonstrated in orbital fibroblasts, it is conceivable that the TSH receptor be involved in the pathogenesis of GO as well [15]. This seems to be further supported by a recently established murine model of GO induced by thyrotropin receptor plasmid in vitro electroporation [16]. The IGF-1 receptor (and related autoantibodies) might also be involved in the pathogenesis of GO, as suggested by several lines of circumstantial evidence [17]. It remains to be established whether autoimmunity to the TSH receptor is the primary event and autoimmunity to the IGF-1 receptor is a secondary phenomenon important for maintaining ongoing reactions [18].

### Clinical manifestations and diagnosis

Common symptoms include diplopia, or symptoms related to exophthalmos and corneal exposure, such as photophobia, tearing, grittiness, and pain [3]. Diplopia classified as intermittent (present when the patient wakes up in the morning or is tired in the evening), inconstant (present at extremes of gaze) or constant (present also in primary gaze and/or reading position), is due to extraocular muscle involvement and restrictive ophthalmoplegia. Soft tissues changes, (eyelid edema and hyperemia, conjunctival hyperemia, chemosis, caruncle edema) are frequent, especially in patients with moderate-to-severe and active disease [3] (Fig. 2). The infrequent DON may be heralded by decreased color sensitivity and/or decreased visual acuity and/or visual field defects. Even mild ocular changes (e.g., lid retraction, mild exophthalmos, swelling of periorbital tissues, stare) have a large negative impact on the quality of life [19].

Standardized assessment of GO, as proposed by experts in this field [20, 21] is fundamental to the therapeutic strategy. Patients with GO undergo an initial phase of inflammation (active phase), a subsequent period of stabilization (static phase), and a final inactivation phase (burnt-out disease), almost never associated with a complete remission of ocular changes [3]. Activity of GO can be (imperfectly) assessed by calculation of the Clinical Activity Score (CAS), based on seven items (palpebral edema, palpebral erythema, conjunctival hyperemia, chemosis, caruncle edema, spontaneous ocular pain, pain with eye movements), giving a possible score ranging from 0 (no activity) to 7 (maximal activity) [22]. GO is considered to be active when CAS is $\geq$3. Independently of the activity, GO may be mild, moderate-to-severe, or sight threatening, based on objective evaluation of different ocular

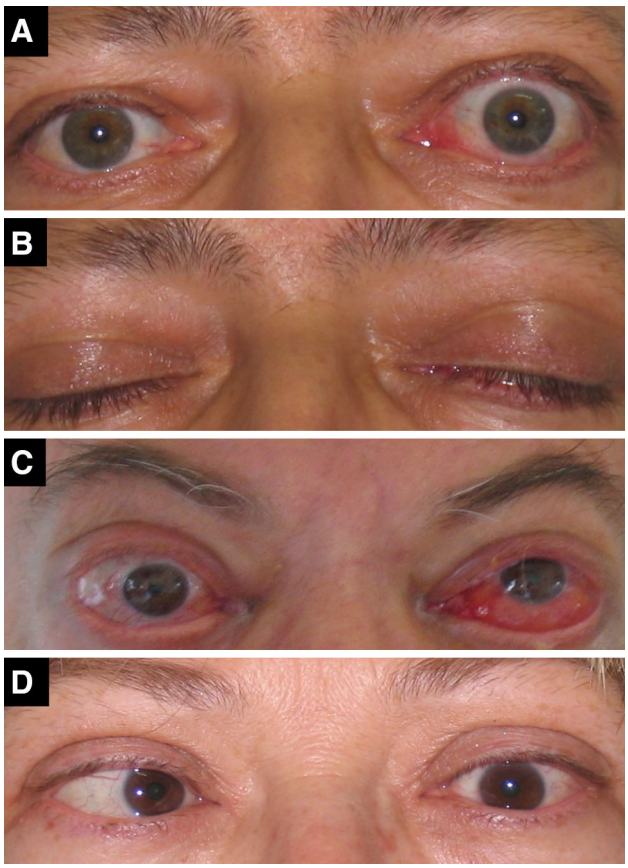


**Fig. 2** Clinical features of Graves' orbitopathy. **a** Mild and inactive GO with exophthalmos and lid retraction in *left eye*; **b** lagophthalmos (incomplete eye closure) in *left eye*; **c** moderate-to-severe GO with marked inflammatory signs (mainly in *left eye*) and deficient movement in upward gaze in *right eye*; **d** strabismus (esotropia) in *right eye*

parameters (soft tissue changes, exophthalmos, extraocular muscle dysfunction, corneal involvement, optic nerve involvement) [23].

## Prevention

While genetic predisposition is ill defined, the role of some environmental risk factors for occurrence/progression of GO is defined better (Table 1) [24]. Identified risk factors include cigarette smoking, thyroid dysfunction (both hyper- and hypothyroidism), radioiodine therapy for hyperthyroidism, higher levels of TSH receptor antibodies, and oxidative stress [24]. Accordingly, patients should be firmly encouraged to refrain from smoking, because quitting smoking has been associated with a decreased risk of developing exophthalmos and extraocular muscle dysfunction [25]. Euthyroidism should be promptly restored and stably maintained, because this may lead to amelioration of GO [26]. Most (if not all) patients treated with radioiodine should receive low-dose oral prednisone (so-called steroid prophylaxis) to prevent radioiodine-induced *de novo* occurrence or progression of existing GO [23, 27, 28]. There is no way to directly reduce TSH receptor antibodies, but control of hyperthyroidism by antithyroid drugs or thyroidectomy is associated with a progressive decrease in their concentration [29]. Both Graves' disease and GO are associated with increased oxidative stress [30]. Selenium is a trace element relevant to thyroid physiology and pathophysiology [31]. Due to its antioxidant and immunoregulatory actions, selenium supplementation has been used in patients with autoimmune thyroiditis with controversial results [32]. Evidence for GO is more encouraging. In patients with mild GO, selenium treatment has been shown in a large-randomized clinical trial to be associated with improvement of GO and reduced risk of progression to more severe forms [33]. Accordingly, selenium supplementation should be regarded as preventive measure in Graves' patients with mild GO, and probably, with no existing GO (Table 1).

**Table 1** Modifiable risk factors for extrathyroidal manifestations of Graves' disease and preventive actions

| | Risk factor | Preventive action |
|---|---|---|
| Orbitopathy | • Smoking | • Refrain from smoking |
| | • Thyroid dysfunction | • Restore euthyroidism |
| | • Radioiodine treatment | • Steroid prophylaxis |
| | • High TSH receptor antibodies | • Restore euthyroidism, possibly elimination of antigen source (thyroid ablation) |
| | • Oxidative stress | • Selenium supplementation |
| Dermopathy | • Smoking | • Refrain from smoking |
| | • Thyroid dysfunction | • Restore euthyroidism |
| | • Trauma or surgery of lower extremities | • Avoid, unnecessary trauma or lower extremity surgery |
| | • Overweight | • Reduce body weight |
| Acropachy | • Unknown (possibly same for other manifestations) | • As for orbitopathy and dermopathy |

## Management

Mild forms of GO do not usually need any treatment, except for local measures (artificial tears, ointments, dark glasses) and preventive measures as outlined above (Table 1) [3]. Occasionally, systemic immunosuppression may be required similar to management for moderate-to-severe and active GO because of impaired quality of life [23].

Treatment of moderate-to-severe GO depends on the activity of the disease. If the disease is stable and inactive,

there is no role for medical treatment, and the patient should be submitted to appropriate rehabilitative surgery (orbital decompression, eye muscle surgery, eyelid surgery, etc.,) (Table 2) [34]. For moderate-to-severe and active GO, systemic glucocorticoids represent the first-line treatment of choice [23] and are preferably given by intravenous route [35]. Oral glucocorticoids are also effective, although less than intravenous glucocorticoids [3]. The cumulative suggested dose of intravenous glucocorticoids varies according to different published series [36]. A recent large-randomized clinical trial showed that a cumulative dose of about 7.5 g of methylprednisolone (distributed in 12 weekly slow infusions) was more effective compared to lower doses (4.5 and 2.25 g), but also was associated with a higher rate of major adverse events [37]. This suggests that the middle dose is probably the best for most patients, while the highest dose should be reserved for most severe cases of GO [37]. In any case, a cumulative dose of 8 g should not be exceeded to minimize the risk of hepatotoxicity [38]. Features of GO with the best response to medical therapy are soft tissue changes, recent onset extraocular muscle dysfunction, and optic nerve involvement, while exophthalmos, lid retraction and longstanding extraocular muscle impairment (associated with fibrotic changes) are unlikely to benefit from treatment [14]. Regrettably, a considerable proportion of patients do not respond satisfactorily to initial treatment [39] and need to be retreated with glucocorticoids, or with other alternative treatments, including orbital radiotherapy (effective especially on ocular dysmotility) [40] or cyclosporine combined with corticosteroids [41]. For other systemic therapies, including somatostatin analogs, methotrexate, azathioprine, intravenous immunoglobulins and apheresis there have been either no demonstrated effectiveness in randomized clinical trials, or no randomized trials are available [3]. At the end, at least 40 % of patients with severe disease after medical management may require surgical procedures and rehabilitation [42]. Should multiple surgeries be needed, orbital decompression should be done first, followed by squint surgery, and, lastly, eyelid surgery [23].

## Thyroid dermopathy

Thyroid dermopathy or PTM is an uncommon autoimmune manifestation of Graves' disease [4, 43, 44]. Characteristic skin thickening in majority of cases is limited to the pretibial area [4]. However, the disorder can occur in other areas such as upper extremity, surgical scars, vaccination sites and areas exposed to trauma or pressure [44].

### Histologic findings and pathogenesis of thyroid dermopathy

There are similarities between histologic features and pathogenesis of GO and PTM [12, 18, 45]. In both conditions, there is accumulation of glycosaminoglycans and mucin materials [46, 47]. In both there is fibroblast proliferation. However in dermopathy lymphocyte proliferation is less prominent. In both TSH receptor in the fibroblasts and its interaction with TSH receptor antibodies provokes cascade of immune process and cytokine reaction with activation and proliferation of fibroblasts and subsequent mucin production. As previously mentioned, recently a role for IGF-1 receptor antibodies in the pathogenesis of extrathyroidal manifestations has been proposed [17, 48].

Peculiar localization of dermopathy to the lower extremities in the form of PTM is more likely related to local mechanical factors, such as dependency, rather than to differences in fibroblasts of different areas of skin [47, 49, 50]. In favor of the mechanical factor theory is the fact that skin grafted to the lower extremity from areas that are not usually involved, may develop thyroid dermopathy at the recipient and donor sites [49, 51]. Dermopathy can also occur at the upper parts of body exposed to trauma or surgery and also in scar tissues [4, 44, 51]. The local accumulation of glycosaminoglycans leads to retention of fluid and expansion of connective tissues similar to what happens in GO [12]. Thus, the characteristic skin changes develop [4, 44]. Obstruction of the lymphatic microcirculation and fibrosis causes progression of lesions and contributes to the development of elephantiasis in advanced

**Table 2** Established treatments for extrathyroidal manifestations of Graves' disease

| | | |
|---|---|---|
| Orbitopathy | • Mild | • Local measures, preventive actions, selenium |
| | • Moderate-to-severe, active | • Systemic glucocorticoids (first-line), orbital radiotherapy, cyclosporine |
| | • Moderate-to-severe, inactive | • Rehabilitative surgery, as needed |
| | • Sight-threatening | • Systemic high-dose glucocorticoids, orbital decompression |
| Dermopathy | | • Local glucocorticoids |
| | | • Systemic glucocorticoids (mainly needed for associated GO) |
| Acropachy | | • None |
| | | • Pain management in rare cases |

cases [49]. Dependency of the lower extremity may be aggravated by obesity. Another environmental factor is tobacco use that is a high-risk factor for all the extrathyroidal manifestations of Graves' disease, including dermopathy and acropachy [52–54]. History of tobacco use is present in 75 % of patients that have dermopathy or acropachy [44, 55].

In summary, with demonstration of TSH receptors in the skin fibroblasts and better knowledge of activation of autoimmune cascade in extrathyroidal manifestations of Graves' disease, and the role of mechanical factors in pathogenesis of thyroid dermopathy, the mechanism for the common location of dermopathy on the pretibial region has been better defined.

### Clinical manifestations and diagnosis

Thyroid dermopathy commonly presents itself in the pretibial area. But involvement of upper body can also occur [43, 44], particularly in areas exposed to repeated trauma, surgical scars, vaccination sites and burn scars, and also in upper extremity skin grafted to lower extremity [51, 56]. Lesions are usually symmetrical in the lower extremity with an appearance similar to orange skin [4] (Fig. 3). Lesions may be raised and firm. They usually have a reddish color but may be pigmented and may also have hyperhidrosis. In pretibial area several forms have been reported. Most common presentations are non-pitting edema and plaque forms. Nodular pretibial dermopathy may also be present. Elephantiasis form is less common and occurs in 5 % of cases (Fig. 3) [4]. Lesions do not ulcerate but may be pruritic. Pain and burning [9] may rarely be present in particular when associated with periostitis of thyroid acropachy [55]. Mild cases are of only cosmetic concerns, but severe cases may create functional problems such as difficulty in wearing shoes [4]. In some cases, entrapment neuropathy and even foot drop have been reported [57].

Presentation of pretibial myxedema in Graves' disease without clear history of GO has been reported [9]. In a case series of 178 patients with thyroid dermopathy, only four patients had no evidence of GO [44]. The onset of thyroid dermopathy follows GO and on the average occurs 12–24 months after the diagnosis of thyrotoxicosis, but can occur many years after diagnosis of hyperthyroidism in some cases [44].

In the presence of GO, the diagnosis of thyroid dermopathy is clear and is based on typical skin lesions. Biopsy is needed only in questionable cases. The diagnosis should be doubted in the absence of GO. Skin changes somewhat similar to those of thyroid dermopathy can occur in various conditions with chronic edema and mucinosis as a result of venous insufficiency, generalized myxedema, chronic or lichenified dermatitis, hypertrophic lichen planus and mucinosis associated with morbid obesity [58]. Absence of GO, lack of history of Graves' disease and, in particular, absence of elevated TSH receptor antibodies should exclude thyroid dermopathy [4].

## Thyroid acropachy

The most common form of acropachy is clubbing of the fingers and toes (Fig. 4) that occurs in 20 % of patients with dermopathy [55]. Swelling of the digits and toes and periosteal reaction of the underlying bones constitutes the

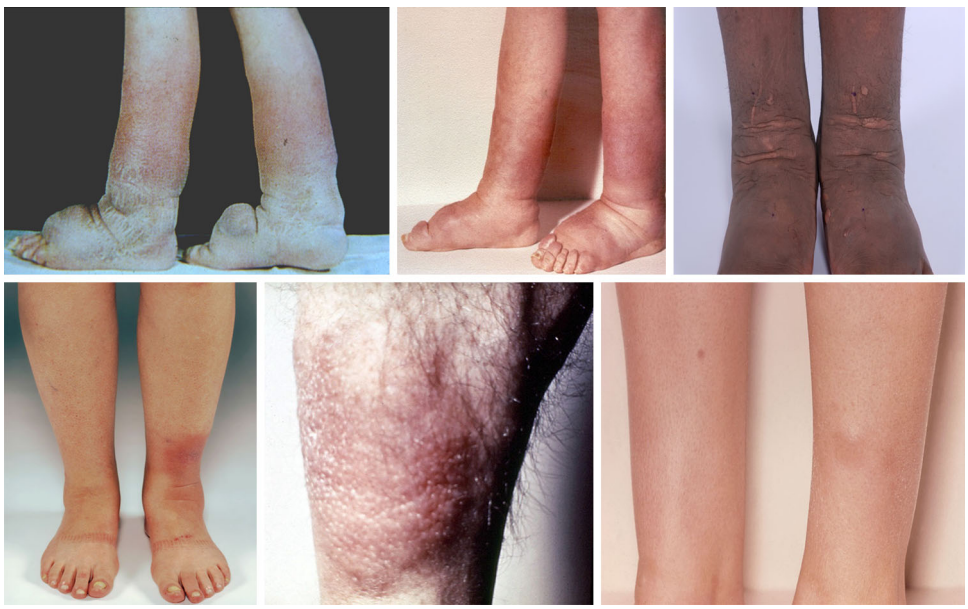

**Fig. 3** Various forms of thyroid dermopathy (PTM)

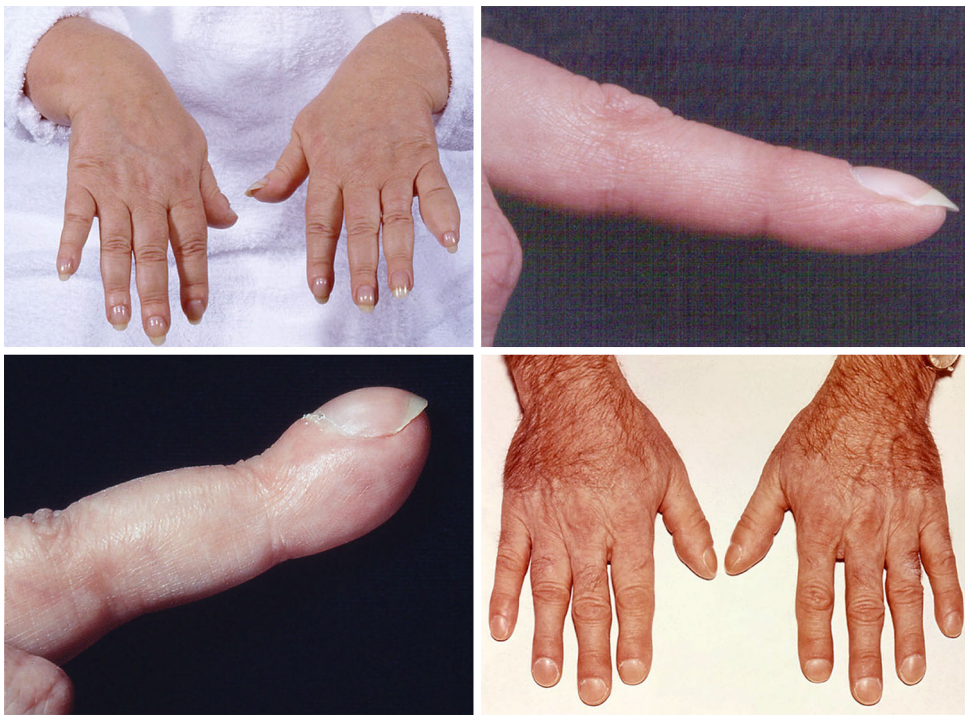

**Fig. 4** Thyroid acropachy in several patients. Note fusiform swelling of the fingers and various degrees of clubbing

full clinical picture and is less common. Acropachy almost always occurs in association with GO and thyroid dermopathy. Joints are not involved, and the local warmth and increased blood flow characteristic of pulmonary osteoarthropathy are usually absent. Acropachy is often painless, but some patients have pain and also loss of function because of extreme swelling [55].

Fusiform soft-tissue swelling of the digits and subperiosteal bone formation of the bones of the hands and feet are the radiographic findings. The subperiosteal reaction is unusual in the long bones of the forearms and the legs [55]. Technetium–pyrophosphate bone scans may show focal accumulation of radionuclide in the affected areas [55].

Histologic skin features in acropachy are similar to those of thyroid dermopathy. For the bony changes, the only available histologic study showed nodular fibrosis of periosteal area with subperiosteal bone formation and fibrosis [59]. Autoimmune activation of periosteal fibroblasts and mucin deposition remains a possibility.

## Prevention of dermopathy and acropachy

All the factors described for prevention of GO are applicable to dermopathy and acropachy. Since patients with GO, in particular with severe GO, are at higher risk of dermopathy, GO patients are candidates for consideration of preventive measures. These measures include tobacco cessation [54, 60] and attention to emotional burden of extrathyroidal manifestations [61, 62]. Optimal management of thyroid dysfunction, rapid normalization of thyroid function, avoidance of persistent hyperthyroidism and early management of treatment-related hypothyroidism are also essential [23, 24, 63, 64]. Theoretically total ablation of thyroid either by surgery, radioiodine or a combination of both, because of elimination of source of antigen, may also be an empiric preventive measure [65–68]. Available data are, however, inconclusive. Whether selenium, shown to be effective on mild GO [33], may have beneficial effects on dermopathy and acropachy is unknown. There are some preventive measures that are specific for dermopathy. They include avoidance of trauma, unnecessary surgery in the lower extremities and weight loss in overweight patients [4, 69].

## Management of dermopathy and acropachy

Although many patients are asymptomatic and lesions are not particularly unsightly, or the lesions can be covered by clothing, local corticosteroid therapy should be started early in the course of the disease to prevent secondary processes such as fibrosis and lymphatic obstruction [44, 70]. Mid-potency corticosteroid fluocinolone acetonide, high-potency clobetasol propionate, or triamcinolone cream base 0.05–0.1 % under Saran plastic wrap occlusive dressing can be used for 12 h/day for 4–6 weeks (Table 2) [4]. Compression stockings with 20–40 mmHg of pressure or intermittent pump as used for lymphedema are also helpful. Complete decompressive physiotherapy (CDP),

manual lymphatic drainage, manual massage, multilayered low stretch compressive bandaging to create a pump under graduated bandage are also beneficial in severe cases including elephantiasic forms (Table 2) [71]. Surgical excision should be avoided because of the possibility of surgical trauma related aggravation. Intralesional multiple injections of a solution of dexamethasone, lidocaine, and saline in the pretibial plaques once a week for 3 consecutive weeks applied with mesodermic needle in five patients were reported to result in significant resolution of dermopathy without development of subcutaneous atrophy or pitting of the skin [72]. These needles deliver the medication within the dermis or the first layer of the subcutaneous fat. Another report also showed similar results [73]. More studies are needed before routine use of this method.

For thyroid acropachy no specific treatment is available other than therapy of basic immune process and management of associated dermopathy. Occasionally painful periostitis of acropachy will require pain management or anti-inflammatory agents [55].

Since majority of patients with dermopathy have relatively severe GO, systemic immunosuppressive therapies used for orbital disease often improve dermopathy. All the systemic therapies discussed for GO are applicable for dermopathy and acropachy not responding to local corticosteroid therapy. Uncontrolled trials of plasmapheresis, high-dose intravenous immunoglobulin have been reported with some benefit on dermopathy, [74, 75]. Because of the small number of reported patients, short follow-up periods, and lack of controlled studies, the evidence related to these therapies remains anecdotal.

Long-term remission appears to depend more on the severity of initial disease rather than on the effect of therapy. About half of patients with mild dermopathy undergo complete remission in long-term follow-up even without specific therapy for dermopathy [44]. The present therapeutic modalities are palliative at best, and better and safer means of immune modulation are needed to treat this and other extrathyroidal manifestations of autoimmune thyroid disease. It is unlikely that randomized trials for dermopathy will be feasible, and thus immunotherapies proven of benefit for GO should also be tried for dermopathy.

## Perspectives

As briefly outlined in this review, pharmacological treatments for extrathyroidal manifestations of Graves' disease are largely imperfect. This is particularly relevant for orbitopathy that is the most common manifestation [76]. Our better understanding of pathogenesis of GO allows envisioning targeted therapies directed against one or more steps involved in the development of orbitopathy [77].

**Table 3** Potential future treatments for Graves' orbitopathy (and other extrathyroidal manifestations of Graves' disease)

| Drug/agent | Target |
|---|---|
| Rituximab | CD-20 positive B cells |
| Adalimumab, etanercept, infliximab, belimumab | Tumor necrosis factor (TNF) |
| Tyrosine kinase inhibitors | Platelet-derived growth factor (PDGF) |
| Tocilizumab | Interleukin-6 receptor |
| TSH receptor-blocking antibodies/ small molecules | TSH receptor |
| IGF-1 receptor-blocking agents | IGF-1 receptor |

There are several potentially useful drugs (Table 3). Among them, rituximab, a drug depleting CD-20 positive B cells, is actively being investigated [78]. Results of preliminary, uncontrolled and small studies (reviewed in [79]) are promising, but results of ongoing randomized clinical trials have not been published. It is not clear yet if this drug might truly represent a useful tool as first-line treatment or it should be used for the management of glucocorticoid-resistant GO [77]. In view of the role played by cytokines, anti-cytokine therapies might be developed in future for GO. In this regard, preliminary results on the use of anti-tumor necrosis factor (TNF) (adalimumab, etanercept) [80, 81] or anti-interleukin-6 (tocilizumab) [82] monoclonals seem potentially interesting. Likewise, tyrosine kinase inhibitors (imatinib mesylate, AMN 107) might find a place in the management of GO, owing to their inhibition of platelet-derived growth factors (PDGFs) [83]. Most importantly, with possible role of the TSH receptors and the IGF-1 receptors in the pathogenesis of GO, these receptors might be targeted by blocking monoclonal antibodies or small molecule antagonists [84, 85].

These potential therapeutic modalities are supported by either in vitro or preliminary in vivo studies. Adequately powered randomized clinical trials, (preferably multicenter, because of relative rarity of extrathyroidal manifestations) are needed to evaluate these agents. Whatever agent proven to be useful for GO can be empirically used for dermopathy.

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**Conflict of interest** None to declare.

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