Summary

Graves’ ophthalmopathy (thyroid-associated ophthalmopathy [TAO]) and dermopathy (thyroid-associated dermopathy [TAD]) are extrathyroidal manifestations of Graves’ disease, which should be viewed as a multisystem autoimmune disease involving thyrocytes but also orbital and pretibial fibroblasts. Smoking is a risk factor for TAO, and cessation of smoking is useful in the primary, secondary, and tertiary prevention of TAO. The immunopathogenesis of TAO and TAD looks very similar. Fibroblasts expressing functional thyroid-stimulating hormone (TSH) receptors have been identified as the target cells of the autoimmune attack. T cells sensitized to thyroid antigens (or TSH receptor stimulating antibodies, TSAb, in later stages) may recognize shared antigens on fibroblasts, inducing release of cytokines. This results in the production of hydrophylic glycosaminoglycans, causing tissue swelling. Recent findings point to the insulin-like growth factor-1 receptor on fibroblasts as another likely autoantigen. TAO appears to be primarily a Th1-cell-mediated disease. Intravenous methylprednisolone pulses are now recommended as the treatment of choice in severe active TAO and topical corticosteroids under occlusive dressings for TAD. Rehabilitative surgery for TAO should wait until the disease has become inactive. Promising new but still experimental treatment modalities involve monoclonal antibodies against particular cytokines or T-cell surface molecules.

Key Words: Thyroid eye disease, pretibial myxoedema, immunopathogenesis, thyrotropin receptor, IGF-1 receptor, treatment, smoking.
INTRODUCTION

Graves’ disease is primarily characterized by hyperthyroidism caused by thyroid-stimulating hormone (TSH) receptor stimulating antibodies (TSAb). Because the autoimmune reaction is directed against the TSH receptor (TSHR) in the thyroid gland, Graves’ disease has been considered as the prime example of an organ-specific autoimmune disease. This view, however, seems to be too restricted as it does not take into account the three extrathyroidal manifestations of Graves’ disease: thyroid-associated ophthalmopathy (TAO), thyroid-associated dermopathy (TAD), and acropachy. The extrathyroidal phenotypes of Graves’ disease cannot be explained by thyroid hormone excess itself. It is doubtful—as will be argued next—whether TSAb can be held fully responsible for the phenotypic variation, although the concentration of serum TSAb in general is higher in TAO and even more so in TAD than in Graves’ hyperthyroidism without extrathyroidal manifestations \(^\text{[1]}\). These kinds of considerations have led some authors to view Graves’ disease as a multisystem autoimmune disease, in which the autoimmune attack is directed not only toward thyrocytes but also against fibroblasts in the orbit and the dermis \(^\text{[2]}\).

The present review is limited to TAO (also known as thyroid eye disease, Graves’ ophthalmopathy, or Graves’ orbitopathy) and TAD (also known as pretibial or localized myxoedema), focusing on advances in knowledge obtained since 1990. Considerable progress in understanding the nature of these conditions has been made, but it is fair to say that TAO and TAD are still one of the remaining enigmas of autoimmune thyroid diseases (AITD) with respect to their immunopathogenesis as well as to their management. This is the more worrisome as the burden of disease of these conditions can be substantial: the health-related quality of life in TAO patients is indeed markedly decreased and lower than that of patients with diabetes mellitus, emphysema, or heart failure \(^\text{[3]}\). A short look at the appearance of extrathyroidal manifestations of Graves’ disease suffices to understand how the cosmetically disfiguring and the functionally invalidating changes can have a serious impact on the patient’s daily life. The NO SPECS classification of eye changes (Table[1]) serves as a mnemonic in the examination of the ophthalmopathy.

EPIDEMIOLOGY

A population-based cohort study in Olmsted Country, Minnesota, reports an overall age-adjusted incidence rate of TAO of 16.0 women and 2.9 men per 100,000 inhabitants per year \(^\text{[4]}\). The incidence rate exhibits an apparent bimodal peak in the fifth and the seventh decade of life. Seventy-four percent of the cases had minor eye changes not requiring specific treatment other than supportive measures. Smoking greatly increases the risk for TAO (odds ratio 7.7, 95% confidence interval [CI] 4.3–13.7), and smokers have more severe eye disease than non-smokers \(^\text{[5]}\). A trend toward a lower incidence rate of TAO has been observed since 1990. In a questionnaire survey among thyroidologists from 15 European countries in 1998, 43% of the respondents thought TAO was decreasing in frequency, 42% thought it unchanged, and 12% thought it to be increasing \(^\text{[6]}\). In this respect, it is noteworthy that all responders from Hungary and Poland, where the population of smokers in the general population had increased since 1990, indicated an increased incidence of TAO. The overall trend toward a lower