

# Cigarette smoking: number one enemy for Graves ophthalmopathy

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Graves ophthalmopathy or orbitopathy (GO) is an autoimmune disorder involving the orbital tissue and characterized by increased orbital content, due to the expansion of the fibroadipose tissue and increased volume of the extraocular muscles.<sup>1</sup> The underlying pathophysiological process explains the clinical manifestations of GO, such as inflammation and edema of soft tissues, exophthalmos, extraocular muscle dysfunction causing diplopia, and, in rare cases, sight loss due to compression of the optic nerve.<sup>1</sup> GO is the most important and frequent of the extrathyroidal manifestations of Graves disease and has profound negative impact on the quality of life of affected individuals.<sup>2</sup>

Graves disease and GO result from a complex interplay between endogenous (nonmodifiable) risk factors (such as age, sex, or genetic factors)<sup>3</sup> and environmental (modifiable) risk factors (such as cigarette smoking, radioiodine, high thyroid stimulating-hormone receptor antibody [TSHR-Ab] levels, or oxidative stress).<sup>4</sup> Cigarette smoking increases the risk of development of severe forms of GO, de novo development or progression of GO after radioiodine treatment, and decreased or delayed response to immunosuppressive treatments for moderate-to-severe and active GO.<sup>4</sup> While antithyroid drugs and thyroidectomy do not appear to carry a risk of progression of GO, radioiodine treatment is associated with low, but definite risk of progression.<sup>5</sup> Under most circumstances, this untoward effect can be prevented by the administration, in at-risk patients, of a concomitant short course of relatively low doses of oral prednisone.<sup>6</sup>

In this issue of the *Polish Archives of Internal Medicine (Pol Arch Med Wewn)*, Czarnywojtek et al<sup>7</sup> report their experience with 106 patients with Graves disease with mild GO, who were treated with high doses of radioiodine (800 MBq) and steroid prophylaxis (starting dose of oral prednisone: 0.3–0.5 mg/kg body weight, gradually tapered down and withdrawn after 6 weeks).

Cigarette smoking did not affect the cure rate of hyperthyroidism, but was associated with progression of GO in some instances at 6-month follow-up evaluation, despite steroid prophylaxis.<sup>7</sup> Surprisingly enough, exophthalmos was one of the features of GO to be mostly affected. No information is provided as to duration of GO in these patients. This is an important aspect because radioiodine-associated progression of GO is more likely to occur in patients with GO of recent onset.<sup>8</sup> In this study, as previously reported,<sup>9</sup> radioiodine treatment was followed by an increase in serum TSHR-Ab concentrations. Interestingly, this increase was more marked in smokers than in nonsmokers.<sup>7</sup> It has not been determined yet whether the increase in serum TSHR-Ab levels after radioiodine is really the culprit for radioiodine-associated progression of GO, because many patients have no changes in their ophthalmic conditions despite the rise in serum TSHR-Ab concentrations, whereas, on the other hand, increased serum TSHR-Ab levels may be found for several years after treatment.<sup>9</sup>

In summary, this interesting study confirms 2 well-established concepts: 1) cigarette smoking is a deleterious factor for GO; and 2) radioiodine treatment bears a risk for GO progression, particularly in smokers. These issues should be carefully considered when dealing with newly diagnosed patients with Graves disease. A possible development of moderate-to-severe and active GO represents a therapeutic challenge, since available treatments are not always fully effective,<sup>6</sup> and a considerable percentage of patients are unsatisfied with treatment outcome.<sup>10</sup>

What should we do, then, based on the results of this and previous studies? Early diagnosis of Graves disease and prompt institution of antithyroid drug treatment is extremely important. Early diagnosis probably contributes substantially to the recent finding that many patients at diagnosis have no GO (75%) or mild GO (20%).<sup>11</sup> In addition, this may contribute to the secular trend

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towards a decrease in the severity of GO in patients referred to tertiary referral centers.<sup>12</sup> Development of an efficient system or referral pathways to specialized centers or thyroid-eye clinics is also fundamental.<sup>13</sup> General practitioners and specialists should refer all patients with GO, except for the mildest cases responding to local measures (eye drops, ointments) or normalization of thyroid function with antithyroid drugs. Prompt restoration and stable maintenance of euthyroidism is essential, because it is associated with lack of progression or amelioration of preexisting GO.<sup>6</sup> In this regard, it is worth underscoring the need to follow newly diagnosed patients frequently, especially during the first phases of the disease, when this is often unstable. The same principle of strict surveillance should be applied to patients receiving radioiodine treatment, to avoid leaving them with uncorrected hypothyroidism.<sup>6</sup>

Among all of the preventive measures, refraining from cigarette smoking is of utmost importance. Although evidence in the literature is limited to a retrospective study, showing that smoking cessation was associated with a decreased risk of developing exophthalmos and diplopia,<sup>14</sup> all patients with Graves disease, irrespective of the presence or absence of GO, should be urged to quit smoking, if necessary with the help of specialized clinics. The prevalence of smokers has lately decreased in most European countries. This trend must be further strongly stimulated by individual physicians as well as by public and institutional organizations.

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