Thiazolidinedione Precipitated Thyroid Associated Ophthalmopathy

R Menaka, M Sehgal, M Lakshmi, A Bhattacharyya

Abstract
Thyroid associated ophthalmopathy (TAO), a cardinal clinical pointer to diagnose Graves’ disease (GD), is seen less frequently in our country than in the West, but can have sight threatening consequences. Smoking, diabetes, male gender, increasing age and radioactive iodine treatment for thyrotoxicosis are known precipitating factors for TAO. We report four cases of thiazolidinediones (TZD) precipitated TAO. All were male, had autoimmune thyroid disease (three had Graves’ disease and one had Hashimoto’s thyroiditis) and type 2 diabetes mellitus (T2DM). They developed eye symptoms three to four months after taking TZDs for glycaemic control. Two of them responded to medical treatment, the other two underwent surgical decompression.

Introduction
Thyroid associated ophthalmopathy (TAO) is characterized by accumulation of hydrated hyaluronic acid in orbital muscles and connective tissues. There is associated expansion of the orbital adipose tissues. TAO may precede, coincide or follow the systemic complications of dysthyroidism. Link between expression of TSH-receptor (TSH-R) and adipogenesis in orbit of patients with TAO has been suggested. Thiazolidinediones (TZD) – peroxisome proliferator-activated receptor-γ (PPAR-γ) ligand agonists - stimulate functional TSH-R expression, thereby inducing recruitment and differentiation of orbital fibroblasts into mature lipid-laden adipocytes. We report here four TZD precipitated TAO cases seen at Manipal Hospital, Bangalore over the last one year.

Case Reports
Case 1
SN, a 55-yr-man, had a five year history of type 2 diabetes mellitus (T2DM) (Fig.1). Six months before presenting to us, he was started on Rosiglitazone (4mg/day) in addition to his preexisting medications (Glibenclamide and Metformin) for improving glycaemic control. He was diagnosed to have Graves’ disease (Grade 1B goiter) eight months back for which he was being treated with antithyroid medications (ATD). He presented to ophthalmologist (LM) with prominence of eyes, grittiness and diminished vision which he had been noticing from past three months, more so in the previous month. On examination he had bilateral proptosis, eyelid retraction & exposure keratitis for which he had undergone tarsorraphy (Figure 1). Extra ocular motility was restricted and his visual acuity was grossly diminished. CT scan of the orbits showed bilateral extra ocular muscle (EOM) thickening with compression & crowding at apex, left eye being affected more than the right. He was clinically and biochemically euthyroid on antithyroid medications. Rosiglitazone was stopped and normoglycemia maintained with insulin, ATD (started seven to eight months back for Graves’ disease) was continued and three cycles of one Gm intravenous methylprednisolone pulse therapy at an interval 15 days were administered. With orbitopathy deteriorating with diminishing vision (left eye - perception of light only and right eye - 6/18 visual acuity), he underwent orbital decompression surgery. At the end of one year he is euthyroid and euglycemic on Carbimazole and Insulin respectively. It has been decided that his Graves’ disease would be managed with medical treatment for a period of 12-18 months.

Table 1: CT scan measurements of orbital muscle – Case 1

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Normal (in mm)</th>
<th>Rt eye (mm)</th>
<th>Lt eye (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial rectus</td>
<td>3.6 – 5.0</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Lateral rectus</td>
<td>2.0 – 5.2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Superior rectus</td>
<td>3.3 – 6.5</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Inferior rectus</td>
<td>3.6 – 6.7</td>
<td>9</td>
<td>3</td>
</tr>
</tbody>
</table>

Fig. 1: Case 1 before and after treatment

Fig. 2: CT scan of Case 3: Thickened muscle belly of EOM

Case 2
SD, 46-yr-man, had Graves’ disease five years previous to the diagnosis of T2DM with no orbitopathy or dermopathy. He was treated with Carbimazole 40mg for a year and was in remission from last four years. On diagnosis of T2DM six months back, he was started on Rosiglitazone 2mg twice a day as first line therapy elsewhere. Three months later he consulted his ophthalmologist with the complaints of bilateral prominence of eyes, redness, irritability and diplopia. There was no visual compromise. When he presented to us he was clinically and biochemically euthyroid. He had proptosis, left eye being more prominent than the right. Visual acuity and fundii were normal. CT scan of the orbits was confirmatory of EOM thickening, more of the left eye than the right (Figure 2, Table 1). Rosiglitazone was withdrawn and he was started with oral Prednisolone 40 mg/day initially for two weeks and gradually tapered and stopped over a period of eight weeks. His TAO was stabilized, asymptomatic till nine months later when last seen by us. His diabetes was controlled
with Glimepiride.

**Case 3**

JJ, 63-yr-man had T2DM for five years and was taking Gliclazide 80 mg and Metformin 500 mg. He had Graves’ disease three years back, treated with Propylthiouracil for 12 months elsewhere and was in remission. He was started on Pioglitazone 30 mg in addition to the other oral hypoglycemic drugs which he took for three months before developing TAO. He presented with chemosis, proptosis and lid retraction. CT scan of the orbits showed EOM thickening, with compression at the apex. He was clinically and biochemically euthyroid. Pioglitazone was withdrawn and three doses of 1 gm intravenous methylprednisolone pulse therapy at fortnightly intervals were given for orbitopathy. He underwent surgical decompression for deteriorating vision, currently his ophthalmopathy is quiet.

**Case 4**

DV, 60-yr-man presented with diplopia, pain in eyes and ptosis (ophthalmopathy) for two months. CT scan showed EOM thickening right more than left. He had T2DM for last eight years and was taking Gliclazide with Metformin in combination twice a day. He was diagnosed to have Hashimoto’s thyroiditis with hypothyroidism six months back and was on daily thyroxine replacement (100 mcg). At the time of presentation he had been taking Rosiglitazone from last three months which was added as his glycemic control worsened. Rosiglitazone was withdrawn from his treatment and he was put on oral steroid, Prednisolone 40 mg for his ophthalmopathy. His TAO is stable off steroid for ten months when last seen in clinic.

**Discussion**

Graves’ disease (GD) is a heterogeneous autoimmune disorder affecting (with varying degrees of severity) the thyroid gland, eyes and skin. Hyperthyroidism, which occurs in almost all patients with GD, is caused by autoantibodies that stimulate the TSH receptor on thyroid cells. Clinically apparent TAO occurs in 25-50% of patients with GD. TAO is considered to be a chronic, autoimmune inflammatory disorder that impacts all orbital tissue sections and results in various eye features, including lid retraction, soft tissue inflammation, proptosis, extraocular muscle dysfunction, corneal involvement and sight loss. In its severe form, which occurs in 3-5% of patients with eye signs, TAO is a potentially sight-threatening disorder requiring active medical and/or surgical interventions. The course of TAO is unpredictable and a rapid worsening can occur at any time, but it is unusual to happen spontaneously after a significant course of stabilized GD. There are two distinct phases of TAO: acute inflammatory phase and the chronic stable phase. Treatments to alter the natural history of orbitopathy like steroids and radiation are best given in the acute phase of the illness whereas treatments to restore function and improve appearance (surgery) are best given in the chronic phase.

A recent addition to the list of precipitating factors for TAO is thiazolidinediones (TZDs). The TZDs are among one of several classes of oral hypoglycemic agents commonly utilized to maintain glycemic control in patients with T2DM. These agents have been shown to be potent agonists of the nuclear hormone receptor, peroxisome proliferator activated receptor-γ (PPAR-γ), which is found predominantly in adipose tissue and plays a dominant role in adipocyte differentiation.

The volume of both retroorbital fibroadipose tissue and extraocular muscles is increased in patients with TAO. The increase in volume of fibroadipose tissue could be due to adipogenesis or adipocyte hypertrophy. Higher levels of the mRNAs for leptin, adiponectin, and PPAR-γ in the fibroadipose tissue have been found in the genetic studies which suggest the increase is due to adipogenesis. The correlation between the increase in mRNA levels for these substances and that for the TSHR suggests that the receptors are located on the same cells. The stimulus that leads to an increase in adipogenesis in the orbits is likely the TSH-receptor antibodies, present in the serum of most patients with ophthalmopathy. The activation of PPAR-γ by its agonist, TZD, stimulates functional TSHR expression, and also induces the recruitment and differentiation of orbital fibroblasts into mature lipid-laden adipocytes. This potential for preadipocyte differentiation is shared with abdominal subcutaneous tissue.

In our patients the temporal relationship of initiation of TZD to optimise glycaemic control and onset of ophthalmopathy (even in cases where thyroid was inactive clinically & biochemically Case 2&3) suggests that TZD played the significant role in the precipitation of TAO. Similar cases of thyroid eye disease exacerbation following the initiation of TZD have been reported in the literature. Dorkhan et al. showed that a subgroup of patients with T2DM, with no evidence of thyroid disorder, treated with pioglitazone had increased eye protrusion. These studies also suggest that inhibition of the adipogenic pathway through the use of a PPAR-γ inhibitor may be a potential future therapy for TAO and the PPAR-γ expression can potentially be utilized as a marker for TAO disease activity. Since all our patients were started on steroids immediately for ophthalmopathy, simultaneous with withdrawal of TZD in view of their deteriorating ophthalmopathy, we cannot comment on the natural history of TZD induced ophthalmopathy.

Further research is required to establish and prove the role of TZDs in TAO. Meanwhile, we suggest TZDs better be avoided for patients with T2DM with active Graves’ disease and in people with autoimmune thyroid disease.

### Table 2: Summary of Cases

<table>
<thead>
<tr>
<th>Age/ Sex</th>
<th>Duration of T2DM</th>
<th>Thyroid diagnosis</th>
<th>Thyroid status at presentation &amp; current treatment</th>
<th>TMA/ TGA</th>
<th>Diagnosis of TAO after TZD</th>
<th>NOSPECS classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>55/ M</td>
<td>5 years</td>
<td>Graves’</td>
<td>Euthyroid with Antithyroid drugs +ve/+ve</td>
<td>6 months</td>
<td>Class 6</td>
</tr>
<tr>
<td>Case 2</td>
<td>46/ M</td>
<td>6 months</td>
<td>Graves’ 5yrs back</td>
<td>Euthyroid, no treatment +ve/+ve</td>
<td>3 months</td>
<td>Class 3</td>
</tr>
<tr>
<td>Case 3</td>
<td>63/ M</td>
<td>5 years</td>
<td>Graves’ 5yrs back</td>
<td>Euthyroid, no treatment +ve/+ve</td>
<td>6 months</td>
<td>Class 6</td>
</tr>
<tr>
<td>Case 4</td>
<td>60 /M</td>
<td>8 years</td>
<td>Hashimoto’s thyroiditis</td>
<td>Euthyroid, on Thyroxine +ve/+ve</td>
<td>3 months</td>
<td>Class 4</td>
</tr>
</tbody>
</table>
References


4. Valyasevi RW, Harteneck DA, Dutton CM, Bahn, RS. Stimulation of adipogenesis, peroxisome proliferator-activated receptor-gamma (PPARgamma), and thyrotropin receptor by PPARgamma agonist in human orbital preadipocyte fibroblasts. *J Clin Endocrinol Metab* 2002;87:2352–8
