High IOP in Thyroid Eye Disease:
to Treat or not to Treat?

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Overview of the Presentation

1. Thyroid Eye Disease (TED), in Brief

2. Ocular Hypertension in TED

3. Glaucoma in TED
1. Thyroid Eye Disease (TED), in Brief
• The thyroid gland produces **T4** and **T3** hormones

• Thyroid stimulating hormone (**TSH**) from the pituitary gland regulates T4 and T3 production by activating a TSH receptor (**TSH-R**) on the thyroid gland

• In turn, via a “**feedback**” effect, T4 and T3 regulate in part the pituitary TSH production
Graves’ Disease
(General Considerations)

- Graves’ disease is an **auto-immune disease**

- The immune system creates antibodies (IgG) called **thyroid-stimulating IgG (TSI)**

- TSI binds to the TSH-receptor (TSH-R) and leads to an increase in T4 and T3 (hyperthyroidism) and to a decrease in TSH
Thyroid Eye Disease (TED)
(General Considerations)

- **Thyroid eye disease (TED)** affects only 25-50% of patients with Graves’ disease

- TED is an organ-specific autoimmune inflammatory disease of the eye and its surrounding tissues, in particular the:
  - Extra-ocular muscles
  - Intra-orbital content

- This can lead to an intra-orbital volume increase and an **intra-orbital pressure elevation**
TED Pathogenesis
(General Considerations)

• Orbital fibroblasts, unlike other fibroblasts, express thyroid-stimulating receptors (TSH-R)

• Thyroid-stimulating IgG (TSI), that is increased in Graves, activates these TSH-R
  – Fibroblast-to-myofibroblast
  – Fibroblast-to-adipocyte
  – Cytokine production
  – Inflammation, oedema
  – Etc.

• Intra-orbital content and intra-orbital pressure increase
A. In Graves’ disease, usually, levels of the thyroid stimulating hormone (TSH) are low and levels of thyroid hormones (T4, T3) are high

B. Orbital fibroblasts, unlike most other fibroblasts of the body, express the thyroid stimulating hormone receptors (TSH-R)

C. In thyroid eye disease (TED), thyroid stimulating IgG (TSI) stimulates thyroid stimulating hormone receptors (TSH-R) on orbital fibroblasts

D. An increase in the volume of intra-orbital content may lead to secondary elevation of pressure within the orbit

E. All of the above are true
First Take Home Message
(Thyroid Eye Disease)

1. TED is an organ-specific autoimmune disease

2. In the pathogenesis of TED, orbital fibroblasts play a major role
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2. Ocular Hypertension in TED
Thyroid Eye Disease (TED)  
*(IOP Increase or More Correctly IOP Fluctuations)*

- IOP increase can be divided in 3 categories:
  - Ultra-short-term IOP increase
    - seconds to minutes
  - Short-term IOP increase
    - hours to days
  - Long-term IOP increase
    - months to years
Thyroid Eye Disease (TED)  
*(IOP Increase or More Correctly IOP Fluctuations)*

- Ultra-short-term IOP increase
  - Friedenswald’s Equation

- Long-term IOP increase
  - Goldman’s Equation
Patient with Thyroid Eye Disease (TED) &

Intraocular Pressure (IOP) is 24 mmHg (Primary Position)
IOP goes up to 38 mm Hg (Up-Gaze Position)

1. Is the IOP increase simply due to a direct eyeball compression?

2. Is the IOP increase due to another mechanism?
Ultra-Short-Term IOP Increase in TED

(Friedenwald’s Equation)

- **Friedenwald’s Equation** *(non-steady state situation)*
  - Applies, for example, for IOP increase observed in eye movements deviating from the primary gaze position
  - Friedenwald’s equation states that the ratio \( \frac{dP}{dV} = K \)
  - \( K \): Rigidity coefficient of the sclera (0.021 mmHg/\( \mu \)L)
  - \( dP \): Change in pressure (mmHg)
  - \( dV \): Change in volume (\( \mu \)L)
  - It explains why a sudden compression of the eyeball by extra-ocular muscles leads to a relative increase in volume (\( \Box dV \)), that will be followed by an IOP spike (\( \Box dP \)) in order to keep the ratio \( dP/dV \) constant
External Compression can not Explain Long-Term IOP Increase in TED

- In contrast to a sudden compression, a sustained compression of the eyeball, will lead to a decrease in IOP (like during tonography)
- Therefore direct external compression of the eyeball, can not explain the chronic (long-term) IOP increase that is observed in TED, as external compression can only account for short-term IOP fluctuations

Recording of changes in IOP during sustained external pressure on the eyeball during tonography
Long-Term IOP Increase in TED  
*(Modified Goldman’s Equation)*

- **Goldman’s Equation** *(steady state situation)*
  - Applies to steady state situations, where the aqueous humor **inflow** equals the aqueous humor **outflow**
  
  $F_{\text{inflow}} = F_{\text{outflow}}$
Long-Term IOP Increase in TED
(Modified Goldman’s Equation)

- **Goldman’s Equation** (steady state situation)
  - Applies to steady state situations, where the aqueous humor **inflow** equals the aqueous humor **outflow**
  - \[ F_{\text{inflow}} = F_{\text{trabecular-episcleral}} + F_{\text{uveoscleral}} \]

  - \( F_{\text{inflow}} \): Aqueous humor inflow rate
  - \( P_{\text{IOP}} \): Intraocular pressure
  - \( P_{\text{EVP}} \): Episcleral venous pressure
  - \( C \): Trabecular facility
  - \( F_{\text{uveoscleral}} \): Uveoscleral outflow
Long-Term IOP Increase in TED
(Modified Goldman’s Equation)

• Goldman’s Equation (algebraic transformation)

\[ F_{\text{inflow}} = (P_{IOP} - P_{EVP}) C + F_{\text{uveoscleral}} \]
\[ F_{\text{inflow}}/C = P_{IOP} - P_{EVP} + F_{\text{uveoscleral}}/C \]
\[ F_{\text{inflow}}/C + P_{EVP} - F_{\text{uveoscleral}}/C = P_{IOP} \]
\[ P_{IOP} = F_{\text{flow}}/C - F_{\text{uveoscleral}}/C + P_{EVP} \]
\[ P_{IOP} = (F_{\text{inflow}} - F_{\text{uveoscleral}})/C + P_{EVP} \]
Long-Term IOP Increase in TED
(Modified Goldman’s Equation)

- **Goldman’s Equation**

\[ P_{IOP} = \frac{(F_{inflow} - F_{uveoscleral})}{C} + P_{EVP} \]

**Intra-ocular Factors**
- \( F_{inflow} \): Aqueous humor inflow rate
- \( P_{IOP} \): Intraocular pressure
- \( P_{EVP} \): Episcleral venous pressure
- \( C \): Trabecular facility
- \( F_{uveoscleral} \): Uveoscleral outflow

**Extra-ocular Factors**
Long-Term IOP Increase in TED
(Modified Goldman’s Equation)

• Goldman’s Equation

\[ P_{IOP} = \left( \frac{F_{inflow} - F_{uveoscleral}}{C} \right) + P_{EVP} \]

There is a direct relationship between the IOP and the episcleral venous pressure \( (P_{EVP}) \)
(~1 mm Hg \( P_{EVP} \approx ~1 \text{ mm Hg} \ P_{IOP} \))
Causes of Increased Episcleral Venous Pressure

• **Venous Obstruction**
  – Thyroid Eye Disease (TED)
  – Retrobulbar tumors
  – Superior vena cava syndrome
  – Cavernous sinus thrombosis

• **Arteriovenous abnormalities**
  – Carotid-cavernous sinus fistula
  – Orbital varix
  – Sturge-Weber syndrome

• **Idiopathic**

\[\text{non-vascular origin}\]
\[\text{vascular origin}\]
Summary of IOP increase in TED

• In TED, extra-ocular muscles infiltration and fibrosis can lead, in non-primary gaze positions, to IOP spikes (>6 mm Hg)
  – This is due to compression of the eyeball by rather rigid extra-ocular muscles (Friedenwald’s equation)

• In TED, intra-orbital content infiltration and fibrosis can lead to chronic IOP elevation
  – This is due to intra-orbital compression of veins leading to an increase in episcleral venous pressure followed by an IOP elevation (Goldman’s equation)
MCQ

A. In thyroid eye disease (TED), chronic intraocular pressure (IOP) increase can not be explained by an external eyeball compression

B. In TED, only IOP-spikes observed in non-primary gaze position can be explained by an external eyeball compression

C. A sustained external eyeball compression will rapidly lead to an IOP decrease, as it is observed during tonography measurement

D. It is an increase in episcleral venous pressure that explains the chronic increase in IOP that can be observed in TED

E. All of the above are true
Second Take Home Message
*(Chronic IOP Increase in Primary Position in TED)*

1. Chronic IOP increase in TED is not due to an eyeball compression!!!

2. Chronic IOP increase is due to an episcleral venous pressure increase
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Prevalence of Glaucoma in TED

- **Ocular hypertension** (OHT) prevalence is **significantly increased** in patients with TED

- However, **glaucoma** prevalence is **not significantly increased** in patients with TED

- Indeed, IOP is only a risk factor for glaucoma, and in TED the IOP increase tends to be limited in time
Glaucoma and TED: Cave!

Nota bene, in an aside, remember and be aware of:

• **TED optic neuropathy** (mainly due to compression of the optic nerve by enlarged extra-ocular muscles) **may mimic glaucomatous defects!**

• In a patient with a TED and a glaucoma, who shows progression of visual field defects **one should not miss a TED optic neuropathy** (could rapidly lead to blindness)
IOP Treatment in TED

• It is usually considered that it is not necessary to treat gaze-dependent IOP spike increase

• When the IOP is chronically increased in primary-gaze position, then treatment may be considered to reduce the risk of:
  – Glaucoma progression
  – Central retinal vein occlusion (CRVO)
Medical Treatment of Glaucoma in TED

• First-line treatment are drugs inhibiting aqueous humor production
  – β-adrenergic antagonists (β-blockers)
  – Carbonic anhydrase inhibitors (CAI)

• Management of intra-orbital inflammatory component, such as with steroids, may also lead to a decrease in IOP as it will decrease episcleral venous pressure
Surgical Treatment of Glaucoma in TED

- In TED, orbital decompression can lead to IOP reduction

- However glaucoma specialists would tend not to consider a high IOP to be a primary indication for orbital decompression unless filtering surgery is required

- This in order to reduce episcleral venous pressure, and thus decrease the risk for choroidal effusion and suprachoroidal hemorrhage that is associated with glaucoma surgery
A. Ocular hypertension (OHT) prevalence is significantly increased in patients with In thyroid eye disease (TED)

B. Glaucoma prevalence is not significantly increased in patients with TED

C. It is usually considered that it is not necessary to treat gaze-dependent IOP spike increase

D. In glaucoma patients who have TED, first-line treatment are drugs inhibiting aqueous humor production

E. All of the above are true
Third Take Home Message

*(Glaucoma in TED)*

1. Prevalence of glaucoma is not increased in TED!

2. First-line treatments are
   - β-blockers
   - Carbonic inhydrase inhibitors (CAI)

Haefliger IO, von Arx G, Pimentel de Figueiredo AR
Pathophysiology of Intraocular Pressure Increase and Glaucoma Prevalence in Thyroid Eye Disease: A Mini-Review
Klin Monatsbl Augenheilk. 2010; 227: 292-293
Thank You for Your Attention