葛瑞夫茲氏眼病變

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摘　要

葛瑞夫茲氏眼病變是成人最常見的眼眶疾病之一，其發生比例佔葛瑞夫茲病病患者中25%~50%。雖然甲狀腺機能亢進大多都可有效的被治療，然而對於臨床醫師而言，葛瑞夫茲氏眼病變的最佳治療方法仍是一大挑戰。葛瑞夫茲氏眼病變的自然病程具有相當的多樣性。因此治療要根據臨床嚴重性和活動性加以評估。治療主要包含儘早控制甲狀腺功能、緩解症狀以及降低眼窩組織間的發炎。有吸菸的患者要積極衛教戒菸。大部分的患者皆爲輕微眼病變，長期追蹤下來並不會更進一步惡化。抗甲狀腺藥物或甲狀腺切除手術不會影響葛瑞夫茲氏眼病變的病程，然而越來越多證據顯示放射線治療可能會使眼病變新產生或更加惡化。藥物方面，類固醇還是爲主要第一線治療，尤其以針劑效果比口服還更有效。在某些臨床狀況下，放射線療法或減壓手術可爲輔助治療。

關鍵詞：葛瑞夫茲氏眼病變 (Graves' ophthalmopathy)
抗甲促素受體抗體 (Anti-TSH receptor-antibody)

前言

葛瑞夫茲病自西元1835年，由愛爾蘭醫師羅拔．葛瑞夫茲(Robert Graves)發現並以此命名紀念之，已知是一種自體免疫的疾病。臨床表現包含甲狀腺機能亢進、眼睛病變及脛前黏液水腫的皮膚病變。葛瑞夫茲氏眼病變又被稱爲甲狀腺相關眼病(Thyroid associated ophthalmopathy)或甲狀腺眼疾(Thyroid eye disease)。除了影響病人身體不適、容貌外觀外，也是一個潛在威脅視力及降低生活品質的眼部疾病[1]，至今困擾了臨床醫生近兩個世紀。甲狀腺機能亢進大多都可有效的被治療，然而葛瑞夫茲氏眼病變的最佳治療方法仍是臨床一大挑戰。本篇文章將針對葛瑞夫茲氏眼病變相關的自然病程、臨床表現、危險因子、最新進展的病理機轉、及目前與未來最適當的治療方式之臨床證據，作一重點性的文獻回顧。

自然病程

葛瑞夫茲病患者中大約有25%~50%會發生葛瑞夫茲氏眼病變。每年眼病變的發生率在十萬名女性中大約爲16人，在十萬名男性中大約爲3人[2]。將近70%臨床無症狀的患者透過超音波、電腦斷層掃描或眼眶核磁共振影像發現眼外肌肥大的證據[3,4]。葛瑞夫茲氏眼病變大多發生在葛瑞夫茲甲狀腺機能亢進病患，然而有5%~10%病人是發生在甲狀腺低下或甲狀腺機

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能正常身上，其抗甲促素受體抗體（anti-TSH receptor-antibody）的效價濃度比甲狀腺亢進病人來的較低[5]。大約85%病患中，其雙眼的症狀和甲狀腺功能亢進最常見同時發生，或在彼此症狀發作18個月內，然而偶爾葛瑞夫茲眼病變會在甲狀腺機能亢進症之前或之後的多年發病[6]。

臨床表現

將近一半葛瑞夫茲甲狀腺機能亢進病患會主訴眼病變的症狀，包括乾眼、異物感、畏光、過度流淚、複視及眼後窩壓力感。最常見的臨床特點是上眼瞼攣縮(eyelid retraction)導致眼白露出，看起來像在瞪人的錯覺，或是眼眶周圍組織水腫、結膜充血紅腫以及眼球突出。大約3~5%的葛瑞夫茲眼病患者有更嚴重的症狀包含劇烈的眼睛疼痛、發炎、威脅視力的角膜潰瘍或壓迫性視神經病變[7]。凸眼的程度主要取決於眼窩的深度、眼外肌肉、眼後纖維及脂肪組織腫大程度。凸眼的表現通常是對稱但也可非對稱性發生。臨床上可以客觀的使用赫特氏眼外測量計(Hertel exophthalmometer)是用來量側眼緣到角膜頂端的距離，在白人正常上限是20mm，黑人22mm，東方人爲16mm。

臨床分級

目前對評估葛瑞夫茲氏眼病變的嚴重程度或活動程度並無一致的黃金標準。因此臨床研究中使用各種不同評估模式導致很難互相比較治療效果。目前廣泛性使用的包含美國甲狀腺協會(American Thyroid Association)把眼病變臨床表現分成六級(NO SPECS) (表一)[8]。然而這套客觀的評估系統並不總是令人滿意，因爲NOSPECS分類並非每一級都有發炎症狀，無法評估眼病變的活動性。因此目前比較常用Mourits提出的臨床活動分數(clinical activity score)來評估(表二)[9]。每項各算一分，若分數大於等於三分就表示目前處於活動期。2008年歐洲集團針對葛瑞夫茲氏眼病變治療的共識聲明[Consensus statement of the European Group on Graves' orbitopathy (EUGOGO)]中，把嚴重程度分成三類，包含輕度、中度到重度及威脅視力之葛瑞夫茲氏眼病變(表三)[10]，做爲治療上的指引評估。

表一：美國甲狀腺協會葛瑞夫茲氏眼病變的分級（NO SPECS）[8]

分級	定義
0	沒有任何症狀或徵象 (No symptom or sign)
1	只有徵象，沒有症狀(例如眼瞼攣縮、眼瞼遲滯或凸眼到22mm) (Only sign, no symptom)
2	軟組織的侵犯(Soft tissue involvement)
3	凸眼 >22 mm (Proptosis)
4	眼球外肌侵犯 (Extraocular muscle involvement)
5	眼角膜的侵犯(Corneal involvement)
6	視力受損(視神經侵犯) (Sight loss)

表二：Mourits臨床活動分數(clinical activity score, CAS)[9]

1	自發性眼球後疼痛
2	眼球轉動時疼痛
3	眼瞼紅斑
4	眼瞼水腫
5	結膜充血
6	結膜水腫
7	內眥的淚阜(caruncle) 及/或褶襞(plica)水腫
臨床活動分數 ≧ 3/7表示活動期	

表三：葛瑞夫茲氏眼病變嚴重程度分類(EUGOGO)[10]

1. 威脅視力：病人有甲狀腺異常之視神經病變(dysthyroid optic neuropathy)及/或角膜損毀(corneal breakdown)。這類病人必須立即介入治療。
2. 中度到重度：患者通常有以下情況 (≧一項)：眼瞼攣縮≧2mm、中度或重度的軟組織侵犯、與相同種族和性別比較起來，眼球突出≧3mm、恆久性或非恆久性的複視。這類病人眼病變已對日常生活造成足夠影響，須評估免疫抑制療法（活動期）或手術介入性治療（非活動期）的風險。
3. 輕度：患者通常有以下情況 (≧一項)：眼瞼攣縮＜2mm、輕度軟組織侵犯、與相同種族和性別比較起來，眼球突出＜3mm、暫時性或沒有複視、角膜暴露對潤滑劑使用有反應。這類病人眼病變對日常生活通常只有輕微影響，不需使用免疫抑制療法或手術介入性治療。

危險因子

很多的危險因子可能會增加眼病變的風險，分別就以下討論。

一、基因

雖然在文獻上對葛瑞夫茲甲狀腺機能亢進病患的遺傳傾向已被確立，然而遺傳因素在葛瑞夫茲氏眼病變發展的確切角色仍然未知[11]。葛瑞夫茲病的遺傳研究已經證明了同卵雙胞胎共病率(concordance rate)大約30%~40%，而異卵雙胞胎的研究顯示較低的共病率，約5%[12,13]。雖然有一些葛瑞夫茲氏眼病變的基因座(loci)曾被提 出 [human leucocyte antigen (HLA, 6p21.3)，cytotoxic T-lymphocyte antigen-4 (CTLA-4, 2q33), tumor necrosis factor (TNF, 6p21.3), interferon-γ (12q14), intercellular adhesion molecule 1 (ICAM-1, 19p13), thyroid stimulating hormone receptor gene (TSH-R, 14q31)][11]。然而這些結果都不能在大型的研究中被證實或再複製出來，這可能是葛瑞夫茲病和葛瑞夫茲氏眼病變兩者都是臨床異質性很高的疾病，因此很難進行大規模的研究。或者眼病變可能主要受環境因素的影響，而不只是遺傳傾向[12]。

二、性別

就像葛瑞夫茲病一樣，葛瑞夫茲氏眼病變女性比男性還常見，然而長期追下來發現，男性眼病變嚴重程度有較增加的情況[13]。對此的解釋可能是男性往往有更嚴重的甲狀腺疾病導致，然而眞正原因還是不清楚。

三、抽菸

抽菸已被證實是葛瑞夫茲氏眼病變最強且可被修正的危險因子。在荷蘭一項大型的研究中發現，抽菸者比上不抽菸者的勝算比(odds ratio)高達7.7倍[14]。抽菸者的眼病變程度較嚴重且對免疫抑制劑的反應也較差[15]。每天抽菸的次數也與日後發展葛瑞夫茲氏眼病變的可能性也被證實爲一劑量相關性(dose-response relationship)[16]。對於接受放射性碘治療甲狀腺機能亢進的病人，抽菸也會增加日後進展到葛瑞夫茲氏眼病變的可能性[17-19]。在一些回顧性的研究也發現戒菸者的眼病變有比較好的預後[16]。吸煙與許多自身免疫性疾病相關，也許是透過非特異性抑制T細胞活化，減少自然殺手T細胞以及讓體液和細胞免疫受損[20]。葛瑞夫茲氏眼病變和吸煙之間的強力關聯性，除了與香煙毒素的直接效果外[21]，也許還有其他因素的參與。體外試驗資料顯示，香煙的煙霧會刺激眼窩纖維母細胞分泌葡萄糖胺聚糖(glycosaminoglycans, 簡稱GAG)和誘導脂肪細胞分化，也是呈現一種與劑量相關的方式[21]。因此，所有葛瑞夫茲病的患者應被告知吸煙對眼病變的風險性，如果建議戒菸無效，應考慮轉介到戒菸門診或給於其他戒菸策略。

四、甲狀腺機能狀態

甲狀腺功能異常與葛瑞夫茲氏眼病變彼此間是兩個獨立的臨床過程，然而治療甲狀腺機能亢進卻可能對後續眼病變進展過程有著重要的影響。患者如果有控制不良的甲狀腺功能(包含甲狀腺機能亢進或低下)證實比甲狀腺機能正常的患者有更嚴重的眼病變[22,23]。因此建議所有眼病變的患者應迅速恢復甲狀腺功能正常且穩定的狀態，在治療的初始階段，預期甲狀腺功能會有所變化，因此頻繁監測甲狀腺功能是有必要的(每4-6週)。

五、葛瑞夫茲病治療方式

抗甲狀腺藥物[19,24]或甲狀腺切除手術[18,25-27]都不會影響眼病變的臨床病程。也沒有哪種特定的抗甲狀腺藥物或任何形式的甲狀腺切除手術(甲狀腺全切除或次全切除)被證實對預後有任何優勢。然而有少數隨機對照研究指出，放射性碘治療卻對眼病變有所影響。在放射線碘治療後的六個月內，大約有15%患者會產生新的眼病變或對已存在的眼病變更進一步的惡化[17-19]。大約有5%患者在一年後有持續性惡化的狀況，需要額外的治療[17]，然而這種風險在大約給了3個月短期療程的口服葡萄糖皮質素(Glucocorticoids)[17,19]，同時避免放射碘治療後產生的甲狀腺低下問題[23]，幾乎都可消除後續惡化的風險。因此對於活動期的眼病變的患者，建議在放射性碘治療後1~3天，給予預防性類固醇(0.3~0.5mg prednisolone/kg/day)，在三個月內漸漸減藥直到停藥[10]。

如果病患是屬於無活動期的眼病變，並且無其它會惡化的因子，例如抽菸[28]或有高的抗甲促素受體抗體(>7.5IU/L)[29]，那基本上對已存在眼病變的惡化危險性幾乎可以忽略[30-32]。而這類病人並不需給與預防性類固醇的治療[10]。

六、抗甲促素受體抗體(anti-TSH receptor-antibody)

長期以來已知抗甲促素受體抗體效價濃度與葛瑞夫茲病嚴重的病例呈現高度相關。對眼病變也是一個獨立的危險因子。隨著這些抗體的測量更加精確，即使在輕度患者上，這些抗體也可做爲長期追蹤眼病變預後評估[29]。

七、其他

包含年紀(大於60歲)[13]和壓力。

病理機轉

目前的證據指向眼窩纖維母細胞(orbital fibroblast)主要爲造成葛瑞夫茲氏眼病變的標靶細胞，認爲是透過自體免疫的機制使它們正常的功能失調[12,33]。纖維母細胞蛋白質爲自體抗原的這個概念來自於研究發現，當把眼病變患者的T細胞在體外接觸到自體眼窩纖維母細胞的蛋白質後，T細胞會明顯增生[34]。甲促素受體(TSH receptor)一直被推測是眼窩內自體免疫的標靶目標，也因爲周邊循環發現類甲促素因子(thyrotropin-like factor)的關係，進而解釋甲狀腺亢進與葛瑞夫茲氏眼病變兩者間的關聯性[35,36]。隨後研究也證實，葛瑞夫茲氏眼病變患者的眼窩組織中甲促素受體表現會上升[37,38]，並且在臨床活動性最厲害的案例中其甲促素受體表現的又爲最高[39]。這項發現，加上葛瑞夫茲氏眼病變和葛瑞夫茲氏甲狀腺亢進的密切相關性，以及眼病變患者中有持續上升的抗甲促素受體抗體，所以支持甲促素受體是葛瑞夫茲氏眼病變中主要自體抗原。

葛瑞夫茲氏眼病變中，T細胞的活化是一項很重要的免疫病理機轉。眼窩內CD4+T細胞的活化會藉由表面的CD40 ligand (也叫CD154)和眼窩纖維母細胞表面的共刺激蛋白質CD40結合形成CD40-CD154橋梁，誘導纖維母細胞增生且大量分泌IL-1、IL-6和IL-8[40]；而被活化的T細胞會分泌interferon-γ和tumor necrosis factor-α (TNF-α)。纖維母細胞族群中有一亞族群，其細胞表面會高度表現一種細胞表面標記稱Thy-1(CD90)，而這群Thy-1(+)纖維母細胞透過IL-1、interferon-γ和TNF-α的細胞激素刺激下，進而產生prostaglandin E2、IL-8和透明質酸(hyaluronan)[12,41]。透明質酸是一種親水性很強的葡萄糖胺聚醣(GAG)。GAG累積會使眼窩內滲透壓改變、液體累積增加，進而增加眼內壓。因這些東西累積在正常眼外肌肉纖維和眼窩脂肪細胞間，擴大組織的體積容量，導致臨床上我們看到的眼睛外凸、干擾眼外肌運動以及眼窩內靜脈回流的問題。

這群含Thy-1(+)纖維母細胞本身也會製造transforming growth factor β (TGF-β)，TGF-β不僅會刺激纖維母細胞產生透明質酸外，也會進一步讓Thy-1(+)纖維母細胞分化成肌纖維母細胞(myofibroblasts)，參與發炎、修復和晚期纖維化的過程。纖維母細胞、被活化的T細胞、巨噬細胞和脂肪細胞都會分泌IL-6，IL-6會促進B細胞的成熟與分化成漿細胞(plasma cell)，進而製造出更多的抗甲促素受體抗體。

在眼外肌的纖維母細胞幾乎都是Thy-1(+)，然而在脂肪組織中有將近一半的纖維母細胞缺乏這種細胞標記，而這類Thy-1(-)纖維母細胞也叫前脂肪細胞(preadipocyte)，它們可以分化成成熟的脂肪細胞，同時細胞表面也會看到甲促素受體的表現增加[38,42]。透過這些脂肪細胞的分化，導致臨床上看到眼窩脂肪的增生。

脂肪細胞分化需要生長停滯和誘導轉錄因子，包括過氧化物酶體增殖激活受體γ (Peroxisome proliferator-activated receptor gamma, PPAR–γ)[43]。在葛瑞夫茲氏眼病變中，脂肪細胞積極活化的證據包括早期脂肪細胞基因[43]和其他脂肪細胞相關基因的調節增加，包括PPAR–γ、IL-6、脂聯素(adiponectin)和瘦素(leptin)[44]。PPAR-γ的agonist會刺激脂肪細胞的分化，也會使體外培養的眼窩前脂肪細胞的甲促素受體的表現增加[45,46]。有幾篇文獻曾報導在第2型糖尿病人身上使用了thiazolidinedione的藥物後，使得葛瑞夫茲氏眼病變患者的凸眼症狀更加惡

化[47,48]。眼窩前脂肪細胞對PPAR-γ agonist特別敏感可能是一大特徵，因此selective PPAR-γ antagonist也許是未來潛在性的治療目標[49,50]。

Prostaglandins是體內天然的PPAR-γ ligands，被活化的T細胞透過活化cyclooxygenase-2酵素[51]進而製造釋放prostaglandins，它也被發現會誘導眼窩纖維母細胞的脂肪細胞分化[52]。小鼠胚胎幹細胞中，促甲狀腺激素即使在其他無刺激脂肪細胞分化的因子下還是會刺激脂肪細胞分化，這表示單純活化甲促素受體就會啓動新的脂肪細胞發展[53]。其他研究中也發現，如果把眼窩纖維母細胞轉染甲促素受體活化的突變體，無論是早期的脂肪細胞分化和透明質酸的產生都會受到刺激，這表示抗甲促素受體抗體與甲促素受體結合後，就可直接導致眼病變軟組織變化的特徵[43,45]。

第一型類胰島素生長因子受體（type I insulin-like growth factor receptor, IGF-IR）可能是葛瑞夫茲氏眼病變另一個重要的自體抗原。目前發現患有眼病變的眼窩纖維母細胞比正常的纖維母細胞有更高程度IGF-IR的表現[54]。血清中也發現，有種自體抗體會刺激纖維母細胞分泌IL-16和RANTES (regulated upon activation normal T-cell expressed and secreted)的趨化激素(chemokine)，這些趨化激素會使CD4+T細胞的趨化增加[46]。如果使用抑制IGF-IR的單株抗體或轉染IGF-IR去活化的纖維母細胞突變體，以上的這些效果就會受到抑制，表示這個訊息是透過IGF-IR的媒介傳遞。有學者提出IGF-IR和甲促素受體在物理或功能上也許有相關連性，主要是由共定位研究發現能抑制IGF-IR的單株抗體可以抑制甲促素誘導激酶信息傳遞(thyrotropin induced kinase signaling)[55]。雖然IGF-IR和針對這受體的抗體在葛瑞夫茲氏眼病變似乎有潛在性的重要性，但仍未被其他的研究者證實。

透過了解這些病理變化可以幫助我們指出一些臨床潛在性的治療，不過也表示很難設計出眞正有效的免疫療法[56]。因爲這些造成病態性眼窩改變的免疫傳遞物質同時也在應變性免疫反應(adaptive immune response)中扮演其他角色，因此很難預測出這些生物製劑是否在葛瑞夫茲氏眼病變中如使用在類風濕性關節炎一樣有效[57]。這些生物製劑包含anti-TNF的單株抗體(Infliximab或adalimumab)、anti-TNF receptor生物製劑(Etanercept)、anti-IL-1 receptor antagonist (Anakinra)、anti- IL-6 receptor單株抗體(Tocilizumab)、消除B細胞的anti-CD20單株抗體(Rituximab, ocrelizumab)或是針對T細胞上的CD3單株抗體等等，這些新療法都還需要未來更多隨機對照臨床實驗來加以驗證。

臨床治療

根據EUGOGO共識聲明，在治療前要先評估眼病變的嚴重程度和發炎的活性狀態，來做爲治療分類的評估，分別就以下治療討論。

輕度葛瑞夫茲氏眼病變

類固醇或眼窩放射線治療都不建議使用，這狀態下使用的危險性大於得到的效益，一般建議只要簡單的治療做症狀緩解即可。對於因眼角膜暴露產生症狀(異物感、易流淚、畏光)的病患，建議白天可以使用人工淚液或夜間使用人工淚膏，給予眼瞼無法完全閉合的病患提供眼角膜保護[15]。有複視的病人可以使用遮眼或佩戴三稜鏡改善症狀。夜間睡眠時建議墊高枕頭，使頭部抬高以減緩隔日眼瞼水腫。對於上眼瞼攣縮的病患甚至在有經驗的醫學中心可使用肉毒桿菌來減緩攣縮的情形[58]。最近一篇文獻也探討到在輕度葛瑞夫茲氏眼病變的病患，使用硒(selenium)似乎可以改善生活品質、改善症狀且減緩眼病變的進展，不過將來還是需要更多研究來證實它在臨床上的應用[59]。

葛瑞夫茲氏眼病變是一個自限性的疾病，在缺乏無副作用且有效的治療下，觀察等待對大部分輕微眼病變的病人是一個適當的選擇。然而有少數輕微病患，即使輕微眼瞼攣縮、軟組織水腫、眼凸都可能對生活品質有極大的影響[60,61]，這群病患就須根據個別的情形且評估風險與效益來決定是否給予介入性治療。

中度到重度葛瑞夫茲氏眼病變

這群病人大多都需要治療，除非病患沒有症狀或不願意接受治療。對於活動期的患者才需要接受免疫抑制療法，對於非活動期的患者可以考慮復健性手術(rehabilitative surgery)。

非手術的療法包含類固醇治療和眼窩放射線療法。類固醇使用包含口服、局部(打在眼球後或眼結膜下)和針劑的使用方式。口服類固醇最適當的劑量目前並無一致的標準，有學者建議高劑量長時間的使用一段時間(起始劑量80~100mg prednisolone或1mg/kg body weight)。目前口服類固醇並無隨機且安慰組對照研究。在一些公開試驗或隨機研究中，其中口服類固醇與其他治療比較起來，大約33-63%的病人有良好的反應，特別是對軟組織的變化、近期發生的眼外肌侵犯和甲狀腺異常之視神經病變[62-70]。然而眼病變常常在減藥或停藥後復發，並且常伴隨併發症，長期使用下來也有骨質疏鬆的危險[71]。而類固醇打在眼球後或眼結膜下的局部治療效果證實比口服治療來的差[72]。

目前研究發現針劑類固醇脈衝療法比口服類固醇更有效(反應率80% vs 50%)[62-64,71,73,74]。病人在耐受度上比口服來的好[62, 64]，治療的副作用(56% vs 81%，P<0.01)或需其他額外的治療也比較少。目前建議的針劑劑量爲每一個禮拜施打一次0.5mg methylprednisolone，持續六周，之後劑量減爲每周0.25mg methylprednisolone，持續六周，總共累積劑量爲4.5g[10,75]。如果無臨床反應則建議在每周0.5mg methylprednisolone療程的六周後即可停藥。但有文獻報告大約0.8%病人在累積高劑量針劑類固醇下有急性肝損傷和危及生命肝衰竭的風險[76,77]。有一篇文獻中做了劑量上的比較，一次療程累積劑量如果小於8mg methylprednisolone似乎相對安全[78]，因此臨床上建議methylprednisolone一次療程的累積劑量不要超過8mg。如果病人長期(>三個月)使用口服類固醇(平均每天劑量大於5mg prednisolone)，建議使用雙磷酸鹽(bisphosphonates)或其他抗骨質吸收藥物來降低骨質疏鬆的危險[79]。

眼窩放射線療法的反應率大約在60%[15,74]。傳統治療爲約兩周十次療程給予20Gy累積劑量[80]，然而低累積劑量(10Gy)也被證實一樣有效且病人耐受性更好[81]，但更高累積劑量反而不會更有效[82]。一篇隨機控制的研究中指出，口服類固醇效果與放射線療法反應率兩者並無差別[68]。有文獻中認爲放射線療法可以特別有效改善複視和眼球肌肉的運動[83,84]，但也有文獻質疑它的效果[85]。EUGOGO共識建議活動期患者有複視和眼球肌肉運動侷限的症狀可考慮使用放射線療法。但有其他學者是建議是把放射線療法放在對類固醇或開刀的輔助性治療[86]。這表示將來需要更多大型的研究幫助我們釐清它臨床角色的應用。

目前證據證明合併治療(不論口服或是針劑的類固醇加上放射線療法)都較單一治療效果來的好[65,87]。病人對眼窩放射線療法通常耐受性很好，但很多人可能會產生暫時性眼病變的惡化，這種狀況大多可同時使用類固醇來預防[15,74]。長期性的安全目前的資料是令人安心的[88-90]。而對於小於35歲的患者，致癌風險性理論上似乎存在[80,88-90]，因此這群患者在臨床使用上要格外謹慎。白內障的情形也可能在放射線療後提早發生，但目前手術都可以有效處理。傷及視神經導致暫時性的失明的案例也曾被報告過[91]。有少部分人會發生視網膜小血管的變化，大部分發生在嚴重高血壓和糖尿病患者[92]，因此對於糖尿病視網膜病變或嚴重高血壓的患者，放射線療法被視爲絕對禁忌症[93, 94]。但糖尿病本身即使在無視網膜病變下就可能是發生視網膜變化的一個危險因子[90]。雖然目前證據仍不清楚[89]，但糖尿病無視網膜病變的患者也許可被視爲一種相對禁忌症。

其他的治療包含somatostatin analog[95-98]、azathioprine[99]、ciamexone[99]、pentoxifylline[100]、colchicine[101]和免疫球蛋白[70,102]，目前研究不是無法證實有治療效果或僅有一點治療的邊際效果。有兩篇早期研究比較口服類固醇加上cyclosporin合併療法比單一療法來的有效[66,67]。然而這些都不是我們會使用治療葛瑞夫茲氏眼病變的常規性療法。未來還需要更多的研究幫我們對這些藥物有更明確的定位。

目前較熱門被提及可能有效的潛在性療法包含Rituximab[103,104]和Etanercept[105]，然而目前仍缺乏隨機對照試驗。

威脅視力之葛瑞夫茲氏眼病變

病人如果有甲狀腺異常的視神經病變，類固醇和減壓手術是被證實有效的治療，放射線療法不建議使用。建議第一線治療爲高劑量針劑脈衝式類固醇。立即做減壓手術證實沒有比針劑類固醇得到更好的治療效果，也不會減少減壓手術後後續使用類固醇的需要(手術患者有83%後續需要類固醇，使用類固醇患者56%後續需要手術或放射療法)[106]。在高劑量針劑類固醇使用一到兩周後預期視神經功能會有所進步[107]，如果一到兩周後沒有看到治療效果、效果反應差，或使用類固醇的劑量引起嚴重的副作用，建議立即做減壓手術。

角膜損毀(corneal breakdown)的病人應一律視爲一個急症。眼瞼無法閉合的病患，可以每小時使用局部眼睛潤滑液、保濕性的眼箱、或透過眼瞼縫合術，甚至打肉毒桿菌讓眼睛閉合，直到眼角膜開始癒合[108]。對以上治療無效時須考慮類固醇或減壓手術。在嚴重角膜穿孔或嚴重潰瘍時，除給予適當的抗生素和緊急黏合術外，甚至要考慮羊膜移植術(amnion membrane)或眼角膜移植術。

手術治療

復健性手術(rehabilitative surgery)原則上分爲四期：第一期手術爲眼窩減壓術，主要是將眼窩壁的部分骨頭移除，清除眼窩中增生的脂肪組織，減少眼窩內容物，而使眼球外突的壓力減輕，達到使眼球後縮的目的。第二期手術爲斜視矯正手術，目標爲使病患在正視及閱讀時減少複視情形。第三期手術爲眼瞼矯正手術，主要爲眼裂寬度之調整，放鬆攣縮的上下眼瞼。第四期手術才是外觀性或美容性問題之矯正。而這四期手術的進行需具有階段性，因爲前一期的副作用可能會干擾到下一期的手術。如果嚴重眼突的病患，眼窩減壓的目的只是因爲外觀美容的話，一般建議要至少等到眼病變活性穩定下來。除非緊急手術，手術最適當的時機應在甲狀腺眼疾發炎狀況控制良好至少維持六個月以後，且必需在有適當專家的醫學中心進行。主要手術的適應症包含對類固醇或放射性治療仍無法緩解的眼病變進展，或是嚴重眼角膜潰瘍、感染或視神經的影響已經威脅到視力喪失。

結論

葛瑞夫茲氏眼病變的自然病程具有相當的多樣性。因此治療要根據臨床嚴重性和活動性加以評估。治療主要包含儘早控制甲狀腺功能、緩解症狀以及降低眼窩組織間的發炎。有吸菸的患者要積極衛教戒菸。大部分的患者皆爲輕微眼病變，長期追蹤下來並不會更進一步惡化。抗甲狀腺藥物或甲狀腺切除手術不會影響葛瑞夫茲氏眼病變的病程，然而越來越多證據顯示放射線治療可能會使眼病變新產生或更加惡化。藥物方面，類固醇還是爲主要第一線治療，尤其以針劑效果比口服還更有效。在一些特別臨床狀況下，放射線療法或減壓手術可爲輔助使用。

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Graves' Ophthalmopathy

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Graves' ophthalmopathy (GO) is the most common orbital disease in adults and develops in 25% to 50% of patients with Graves' disease (GD). Although thyroid manifestations of GD can be effectively managed, the optimal treatment of GO has remained challenging. The natural history of GO is variable. Patients should be treated according to the severity and activity of their eye disease. Treatment should include control of thyroid function, relief of symptom and reduction of inflammation in the periorbital tissues. Smoker should be educated to quit smoking aggressively. Most patients have mild disease and do not have progression during follow-up. Anti-thyroid drugs and thyroidectomy do not have a negative influence on the course of GO. However, there is increasing evidence that radioiodine therapy can cause the development or worsening of GO. Glucocorticoids(GCs) are the preferred first-line treatment for moderate and severe GO. IV GCs is more effective than oral GCs. Radiation and surgical decompression can also be used in selected patients. (J Intern Med Taiwan 2012; 23: 9-20)