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**Detecção da neuropatia óptica distireoidiana pela
quantificação dos músculos extra-oculares e da gordura
orbitária na tomografia computadorizada**

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Programa de Oftalmologia

Orientador: Prof. Dr. Mário Luiz Ribeiro Monteiro

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Resumo

Gonçalves ACP. *Detecção da neuropatia óptica distireoidiana pela quantificação dos músculos extra-oculares e da gordura orbitária na tomografia computadorizada* [tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2012. 88p.

OBJETIVO: avaliar a capacidade de índices de preenchimento muscular da órbita, calculados a partir de medidas na tomografia computadorizada de multidetectores, detectar a neuropatia óptica distireoidiana em pacientes com orbitopatia de Graves.

MÉTODOS: noventa e três pacientes com diagnóstico de orbitopatia de Graves foram prospectivamente estudados. Todos os pacientes foram submetidos a um exame oftalmológico completo e à tomografia computadorizada de multidetectores. Na estação de trabalho do tomógrafo foram calculados índices baseados em medidas lineares, de área e de volume de preenchimento muscular da órbita. O índice linear de Barrett, foi calculado a partir da relação entre a medida dos músculos extra-oculares em cortes coronais no ponto médio do nervo óptico orbitário e o diâmetro da órbita na mesma posição. Nesse mesmo corte coronal uma escala de 0 a 3 foi utilizada para categorizar o grau do preenchimento muscular e de compressão do nervo óptico segundo método descrito por Nugent e colaboradores. Medidas de área foram realizadas de cortes coronais a 12, 18 e 24 mm da linha interzigomática. Três índices de área foram calculados estimando-se a razão entre a área dos músculos extraoculares e a do continente ósseo medidas. Herniação de gordura orbitária pela fissura orbitária superior foi registrada como presente ou ausente conforme método descrito por Birchall e colaboradores. Dois índices volumétricos foram calculados, o primeiro baseado em cortes axiais de todo o continente orbitário (do ápice à rima orbitária anterior) e o segundo baseado em cortes coronais da órbita a partir de um ponto médio do segmento orbitário do nervo óptico até o limite anterior do canal óptico. As órbitas foram divididas em dois grupos, um com e outro sem neuropatia óptica distireoidiana e esses grupos foram comparados entre si. **RESULTADOS:** cento e duas órbitas de 61 pacientes atenderam aos critérios de inclusão e foram analisadas. Quarenta e uma órbitas eram do grupo com neuropatia e 60 daquele sem a neuropatia óptica distireoidiana. Para todos os índices, exceto para o de herniação de gordura, houve diferença significativa entre os dois grupos ($p < 0,001$). A melhor combinação de sensibilidade e especificidade para o índice linear de Barrett foi de 79% e 72% respectivamente, com razão de chances de 9.2. A escala categórica de Nugent apresentou sensibilidade de 58,3% e especificidade de 84,7%, acurácia de 74,7% e razão de chances de 7,8. Todos os índices de área e de volume apresentaram boa capacidade na detecção da neuropatia óptica distireoidiana. Os índices com melhor desempenho diagnóstico foram o de área a 18mm com sensibilidade de 91,7%, especificidade de 89,9%, acurácia de 90,5% e razão de chance de 97,2, e o de volume do ápice orbitário com sensibilidade de 92%, especificidade de 86%, acurácia de 88% e razão de chance de 97,2. **CONCLUSÕES:** os novos índices calculados baseados em área e volume foram preditores da neuropatia óptica e apresentaram desempenho superior aos métodos reproduzidos de estudos anteriores. A continuidade dos estudos na busca de métodos objetivos e capazes de identificar a neuropatia óptica distireoidiana com cada vez maior eficiência e praticidade é de grande relevância para a melhoria do diagnóstico e do tratamento da orbitopatia de Graves e suas complicações.

Descritores: 1.Oftalmopatia de Graves 2.Neuropatia óptica 3.Tomografia computadorizada multidetectores 4.Órbita

Summary

Gonçalves ACP. *Predicting dysthyroid optic neuropathy using computed tomography quantitative analysis of extraocular muscles and orbital fat* [thesis]. São Paulo: “Faculdade de Medicina, Universidade de São Paulo”; 2012. 88p.

PURPOSE: to evaluate the ability of orbital apex crowding indexes, calculated with multidetector-computed tomography (MDCT), to detect dysthyroid optic neuropathy (DON). **METHODS:** ninety-three patients with GO were studied prospectively with complete neuro-ophthalmic examination and MDCT scanning. All patients underwent a complete neuro-ophthalmic examination and scanning on a MDCT. In a dedicated workstation, linear, square and volumetric indexes of the orbital apex crowding were calculated. Barrett’s linear index was calculated as the percentage of the orbit occupied by muscles in a coronal scan halfway between the posterior globe and the orbital apex. At the same coronal scan, the severity of optic nerve crowding was also assessed by using the subjective grading scale (0, 1, 2 or 3) described by Nugent et al. Quantitative square area measurements were performed on coronal sections 12, 18 and 24 mm from the interzygomatic line. The muscular/bony area ratio was calculated as a crowding index. Intracranial fat prolapse through the superior orbital fissure was recorded as present or absent, according to a method described Birchall et al. Two volumetric indexes were calculated, one from axial scans of the entire orbit content (up to the orbital rim) and one from coronal scans of the orbital content from the entrance of the optic canal up to the middle point of the orbital segment of the optic nerve. Orbits were divided into two groups: with or without DON and comparison between groups was performed. **RESULTS:** one hundred and two orbits (41 orbits with DON, and 61 without DON) of 61 patients met the inclusion criteria and were included in the analysis. All indexes, except the intracranial fat prolapse, were significantly greater in orbits with DON ($p<0,001$). There was no significant difference regarding intracranial fat prolapse. Area under the receiver operating characteristics curves was 0.91, 0.93 and 0.87 for CIs at 12, 18 and 24 mm, respectively. The best combination of sensitivity and specificity for the Barrett’s index was 79%/72% and odds ratio of 9.2. The Nugent’s subjective grading scale detected DON with 58.3% sensitivity, 84,7% specificity, 74.7% accuracy and odds ratio 7.8. All square area and volumetric indexes calculated presented good ability to detect DON. The best performance of the square area indexes was observed at 18 mm where a cutoff value of 57.5% showed sensitivity of 91.7% and a specificity of 89.8%, accuracy 90.5% and odds ratio of 97.2. The best sensitivity/specificity ratio of the volumetric indexes was found for the one calculated at the apex, with sensitivity of 93%, specificity of 84%, and accuracy of 88% for detecting DON. **CONCLUSIONS:** The new orbital crowding indexes based on area and volumetric measurements found to predict DON more reliably than Barrett’s linear index, subjective grading of orbital crowding or intracranial fat prolapse. Further imaging studies would be useful to validate and improve objective methods to predict DON, and thus contribute to early diagnosis treatment.

Descriptors: 1.Graves’ ophthalmopathy 2.Optic neuropathy 3.Multidetector computed tomography 4.Orbit

1 INTRODUÇÃO

Em um curto período, entre 1802 a 1840, quatro médicos de países distintos (Parry na Inglaterra, Flajani na Itália, Basedow na Alemanha e Graves na Irlanda) descreveram independentemente uma doença até então desconhecida caracterizada por taquicardia, bócio e exoftalmo. A princípio, sua causa foi atribuída a uma alteração cardíaca, mais tarde a uma descarga nervosa simpática e, enfim, à hiperfunção tireoidiana.⁽¹⁾ Atualmente, essa afecção tem nomenclatura variada na literatura, sendo geralmente chamada de doença de Graves na literatura americana ou doença de Basedow-Graves na literatura européia.⁽²⁻⁴⁾ Suas características peculiares tem tanto fascinado quanto frustrado a comunidade médico-científica nestes dois séculos de estudos em busca de sua melhor compreensão.⁽⁵⁾

A doença de Graves (DG) é uma das doenças endócrinas mais comuns. Sua ocorrência é de seis a oito vezes mais comum no sexo feminino do que no masculino e ocorre geralmente entre a quarta e a sexta década de vida, sugerindo que um fator indeterminado, relacionado à idade e/ou a fatores hormonais, pode contribuir no aumento de suscetibilidade à doença.⁽⁶⁾

Trata-se de uma doença bem caracterizada, geralmente diagnosticada com base na história e no quadro clínico. Entretanto, dados laboratoriais e radiológicos provêm importantes informações comprobatórias. Essa doença representa um processo autoimune em que o alvo é a glândula tireoide. Nessa glândula, anticorpos estimulantes se ligam a receptores do hormônio tireoestimulante (TSH, do inglês *Thyroid-stimulating hormone*) e amplificam sua função, levando ao hipertireoidismo,

geralmente associado à tireomegalia. A DG é acompanhada de uma série de sintomas relacionados diretamente ao excesso de hormônio tireoidiano circulante. Muitas vezes essa afecção também se manifesta em regiões localizadas do sistema conectivo, incluindo a orbitopatia de Graves (OG) e a dermopatia pré-tibial distireoidiana. Essas manifestações são decorrentes do processo autoimune da DG e não uma consequência do hipertireoidismo. A positividade sérica dos anticorpos antirreceptores de TSH (TRAb) e antitireoperoxidase (TPO) é comum nessa afecção, assim como, numa menor proporção, o anticorpo antitireoglobulina (TG).^(6, 7)

A OG é a manifestação extratireoidiana de maior relevância da DG.⁽⁸⁾ A íntima associação entre o início do hipertireoidismo da DG e o desenvolvimento da OG sugere que essas duas condições compartilham mecanismos patogênicos. Como os anticorpos antirreceptores de TSH (TRAb) são conhecidamente fatores causais do hipertireoidismo na DG, a investigação desses na patogênese da OG é de grande importância.⁽⁵⁾ Entretanto, outros antígenos parecem também participar na iniciação e progresso do processo inflamatório orbitário.⁽⁸⁾

O tecido conectivo orbitário, que envolve os músculos extraoculares e organiza a gordura orbitária, parece ser o alvo primário da autoimunidade.⁽⁹⁾ O fibroblasto presente nesse tecido conectivo expressa receptores de TSH com características semelhantes aos receptores no tecido tireoideo. Vários estudos demonstraram que os fibroblastos orbitários, especialmente os de pacientes com OG, são singulares com respeito a suas respostas a citocinas inflamatórias.^(10, 11) Ademais, a heterogeneidade fenotípica e a dinâmica diferenciação dessas células na órbita podem ser a causa das diferentes manifestações clínicas da doença.^(12, 13)

A progressão da OG não é um processo linear. Parece ser um ciclo de *feedback* positivo composto por fatores mecânicos, imunológicos e celulares. Os sinais e sintomas da OG podem ser explicados mecanicamente pelo desequilíbrio entre o aumento do volume dos tecidos moles orbitários edemaciados e o rígido continente ósseo. O edema inflamatório orbitário desloca o bulbo ocular anteriormente e reduz a drenagem venosa orbitária. Essas alterações, juntamente com atividade das células inflamatórias que infiltram a órbita, como aquela dos fibroblastos que produzem citocinas e outros mediadores inflamatórios, resultam em proptose, edema periorbitário, dor, injeção conjuntival e quemose.⁽¹⁴⁾

O quadro clínico da OG é variável, desde alterações subclínicas a deformidades graves. Incluem-se no quadro clínico: retração palpebral, proptose, estrabismo restritivo, quemose, lesões da superfície ocular e neuropatia óptica.⁽¹⁵⁾

A OG se manifesta com diferentes combinações desses sinais e sintomas. Clinicamente, o espectro dessas combinações se manifesta pelos dois polos clínicos da orbitopatia: o miogênico e o lipogênico. No primeiro tipo o aumento dos músculos extraoculares é o fator principal na gênese do quadro clínico de proptose e estrabismo restritivo. No segundo tipo o aumento dos músculos extraoculares é discreto e o quadro clínico de exoftalmo sem restrição da motilidade ocular decorre principalmente do aumento do volume da gordura orbitária. Mulheres e jovens tendem a se aproximar do polo lipogênico, enquanto homens e idosos tendem a apresentar aumento muscular importante sem muita alteração de volume gorduroso.⁽¹⁶⁾

São dois os estágios da doença. Existe uma fase ativa na qual o processo inflamatório está presente, as alterações orbitárias evoluem e o paciente tem maior sintomatologia. Essa fase tem um caráter autolimitado e não apresenta uma relação

temporal definida com a atividade da DG.^(7, 17) Os processos de atividade da OG e da DG geralmente coincidem, uma vez que dividem uma mesma origem imune, mas não é raro o diagnóstico da OG anos antes ou depois da DG. O estágio final é um quadro clínico estável referente às sequelas da fase ativa.^(5, 18)

A neuropatia óptica distireoidiana (NOD) caracteriza-se pelo dano do nervo óptico na OG, sendo sua complicação mais grave. Essa complicação desenvolve-se em torno de 4 a 8% dos pacientes com OG.^(19, 20) A NOD desenvolve-se na fase ativa da OG. Embora essa fase inflamatória tenda a ser autolimitada, a NOD requer pronto tratamento, uma vez que, se não tratada, resulta em uma perda visual progressiva e irreversível em até 30 % dos casos.⁽²¹⁾

Vários mecanismos foram já foram propostos para explicar o desenvolvimento da NOD, sendo o mais aceito a compressão do nervo óptico no ápice orbitário pelos músculos extraoculares aumentados.⁽²²⁻²⁹⁾

A identificação da NOD é primordialmente clínica. Baseia-se nos achados de redução da acuidade visual, na identificação de defeitos nos exames de campo visual ou da visão de cores com placas coloridas de Ishihara ou Hardy-Rand-Rittler, em alterações no exame potencial visual evocado, na detecção de defeito pupilar aferente e na visibilização de edema do nervo óptico no exame de fundo de olho. Entretanto, esses exames clínicos nem sempre fornecem resultados confiáveis, ora por deficiência dos próprios exames, ora por dificuldades do paciente em realizá-los corretamente. O paciente com OG e, principalmente, aquele com suspeita de NOD frequentemente apresentam um quadro congestivo orbitário, alterações na superfície ocular, incluindo lesões corneanas, quemose, entre outras alterações, que dificultam a realização e a confiabilidade desses exames diagnósticos clínicos, particularmente do

campo visual. Portanto, o diagnóstico clínico da NOD pode ser frequentemente equivocado, tornando difícil a distinção entre a suspeita e a certeza de sua existência.⁽³⁰⁾

Nessa perspectiva, os exames de imagem podem ser de grande utilidade, auxiliando na identificação de indivíduos mais susceptíveis ao desenvolvimento da neuropatia, de tal forma a facilitar o seu diagnóstico. Frente à dificuldade clínica, exames objetivos capazes de auxiliar na detecção da NOD são de grande importância.

A tomografia computadorizada (TC) é um instrumento diagnóstico muito importante no estudo da OG, pois, além de delinear muito bem a estrutura óssea e o conteúdo orbitário, fornece detalhes da musculatura extraocular. Trata-se de um exame corriqueiramente solicitado para o diagnóstico, o controle e o planejamento cirúrgico na condução terapêutica da OG.

Por outro lado, a TC também auxilia na classificação das formas da OG e na análise de suas complicações. A TC pode auxiliar na detecção da NOD, visto que o fato de o mecanismo mais aceito da NOD ser a compressão muscular do nervo no ápice orbitário deve-se principalmente a estudos tomográficos.^(29, 31-33)

Os sinais de hipertrofia muscular e aumento da gordura orbitária já foram descritos como as alterações mais características da tomografia computadorizada na orbitopatia distireoidiana desde a década de 1970.⁽³⁴⁾

Na década seguinte foram publicados estudos tomográficos quantitativos, sendo considerados importantes por fornecerem informações mais detalhadas e objetivas sobre o processo miopático.^(20, 29, 32, 35-37) Com a limitação tecnológica das TC da época, esses trabalhos apresentaram-se sem a excelência na precisão, mas indubitavelmente de grande importância. Hallin e Feldon, em 1988, quantificaram por

meio da TC convencional a musculatura extraocular por medidas axiais dos músculos retos lateral e medial, buscando determinar uma localização padronizada para tais medidas.⁽³⁷⁾ Foram pioneiros na análise volumétrica dos músculos extraoculares e sua correlação com a clínica. Barrett e colaboradores, também em 1988, com o uso da TC convencional analisaram as estruturas em cortes axiais e coronais reformados. O índice muscular proposto neste trabalho tem grande valor na literatura, por obter de forma simples um índice muscular linear que apresentou diferença entre grupos de pacientes com orbitopatia de Graves com e sem neuropatia.⁽³²⁾

Nugent e colaboradores,⁽³⁸⁾ em 1990, com tomógrafo helicoidal, obtiveram cortes axiais e coronais de forma direta e descreveram uma escala subjetiva de quantificação do enchimento do ápice orbitário que teve também grande repercussão na literatura.^(24, 30) Esse método apresentou razoável sensibilidade e especificidade para a detecção da NOD.⁽³⁸⁾ Nessa mesma década, em 1996, Birchall e colaboradores descreveram a identificação da herniação de gordura orbitária pela fissura orbitária superior como elemento preditivo da NOD.⁽³⁹⁾ Özgen e colaboradores, também com a TC helicoidal, validaram essas medidas e contribuíram no desenvolvimento do conhecimento na quantificação de estruturas orbitárias no estudo da OG e da NOD.⁽⁴⁰⁾

Mais recentemente, Giaconi e colaboradores calcularam o índice muscular de Barret, a graduação de exoftalmo, como também a identificação de herniação de gordura, além da escala de Nugent de classificação do enchimento muscular no ápice orbitário, e correlacionam esses dados obtidos com o exame clínico. Esse trabalho, também com TC helicoidal, foi útil na confirmação da importância de índices anteriores no estudo da OG.⁽²¹⁾ Em nosso meio, também houve um estudo com TC helicoidal em pacientes com OG, onde as áreas dos músculos retos extraoculares

foram quantificadas independentemente em 5 cortes coronais, a partir do rebordo orbitário lateral, no sentido ântero-posterior. Neste estudo, entre os 4 grupos analisados (1 sem OG, 2 com OG sem estrabismo, 3 com OG e estrabismo e 4 com NOD) foi observado diferença significativa quanto ao preenchimento muscular do ápice orbitário.⁽⁴¹⁾

Assim, observamos que medidas lineares, de área e volumétricas, como também uma graduação subjetiva, foram utilizadas para calcular índices de preenchimento muscular do ápice orbitário a fim de identificar objetivamente a NOD. Essa revisão da literatura também nos permitiu identificar certas dificuldades nos estudos quantitativos da OG. Com TCs mais antigas, a limitação tecnológica no processamento e análise das imagens determinou estudos trabalhosos e pouco reproduzíveis. Os desenhos retrospectivos e não padronizados na aquisição de imagens também foram obstáculos na qualidade desses trabalhos. Portanto, verificamos que, apesar dos relevantes estudos da TC na OG, ainda se faz importante a busca de métodos mais precisos, práticos e reproduzíveis.

Nas últimas décadas houve um grande progresso na tecnologia dos tomógrafos quanto a aquisição e manipulação de imagens. A TC de multidetectores representou um avanço na captação dos dados. O exame tem curta duração, as imagens são obtidas de forma contínua em uma única captação direta com interposição de imagens. Tais características implicam na reconstrução de alta qualidade das imagens em quaisquer planos: coronal, axial e sagital sem interferência de artefatos dentários ou problemas posturais do paciente. As imagens podem ser estudadas em estação de trabalho de forma digital, onde as dimensões lineares ou volumétricas das estruturas são medidas de forma mais precisa e direta.

2 OBJETIVOS

Com base nos conceitos e situações acima descritos, observamos que com a TC de multidetectores seria possível revalidar índices tomográficos prévios e desenvolver novos índices preditores da NOD potencialmente mais eficientes e reprodutíveis na prática médica.

Portanto, iniciamos um estudo prospectivo, em que estudamos quantitativamente as imagens de TC de multidetectores das órbitas de 2 grupos de pacientes OG: o 1º grupo de pacientes com diagnóstico clínico de NOD e o 2º grupo de pacientes sem o diagnóstico clínico de NOD, com medidas do continente orbitário, dos músculos extraoculares e da gordura orbitária. Os objetivos de nosso trabalho foram:

1. Verificar o desempenho diagnóstico do índice muscular de medidas lineares descrito por Barret e colaboradores⁽³²⁾ na detecção da NOD.
2. Desenvolver novos índices de preenchimento muscular do ápice orbitário baseado em medidas de área. Avaliar seus desempenhos na detecção da NOD e compará-los com índices previamente descritos: o índice subjetivo de Nugent⁽³⁸⁾ e o sinal de herniação de gordura descrito por Birchall e colaboradores.⁽³⁹⁾
3. Calcular índices volumétricos de preenchimento muscular e avaliar seus desempenhos na detecção da NOD.

3 REVISÃO DA LITERATURA

A seguir apresentamos um artigo de revisão da literatura que aborda os métodos de imagem utilizados no estudo da OG, com ênfase especial no diagnóstico da NOD.

3.1 Artigo de revisão

Imaging Studies for diagnosing Graves' Orbitopathy and Dysthyroid Optic Neuropathy

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Running headline: **Imaging studies in Grave's orbitopathy**

Imaging Studies for Diagnosing Graves' Orbitopathy and Dysthyroid Optic Neuropathy

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Abstract

Although the diagnosis of Graves' orbitopathy rests mainly on clinical grounds associated to laboratory tests indicative of thyroid dysfunction and autoimmunity, imaging studies such as computed tomography, magnetic resonance imaging, ultrasound and color Doppler imaging play an important role both in the diagnosis as well as in the follow-up after clinical or surgical treatment of the disease. Imaging studies can evaluate morphological abnormalities of the orbital structures in diagnostic workup when a differential diagnosis with other orbital diseases is needed. It may also be useful to distinguish the inflammatory early stage from the inactive stage of the disease. Finally, imaging studies can also be of great help for screening patients that are prone to develop dysthyroid optic neuropathy and therefore enable timely diagnosis and treatment of the condition and avoiding permanent visual loss. Herein we review imaging modalities that aid in the diagnosis and management of Graves' orbitopathy with special emphasis in the diagnosis of optic nerve dysfunction in this condition.

Key words: Graves' Ophthalmopathy; Optic Nerve Diseases; Multidetector Computed Tomography; Magnetic Resonance Imaging; Ultrasonography; Color Doppler Ultrasonography

Introduction

Graves' orbitopathy (GO) is the most common extra-thyroidal manifestation of Graves' disease (GD), occurring in 25-50% of patients with the disease.(1, 2) It may occur during or after the onset of hyperthyroidism and, less frequently, in euthyroid or hypothyroid patients. The close clinical association between immunogenic hyperthyroidism and orbitopathy suggests that the antigen responsible for these diverse conditions may be shared by the thyroid gland and the orbital tissues.(3) The disease has a self-limited active phase that usually lasts 18 to 24 months and abates slowly, followed by an inactive (static) phase.(4) In the active phase, inflammation, accumulation of glycosaminoglycans and increased fat content determine tissue expansion within a relatively fixed space imposed by the bony orbit.

The diagnosis of GO is usually made on clinical grounds. Signs and symptoms of active GO include lid retraction, proptosis, conjunctival injection, chemosis, diplopia, corneal ulceration and, rarely, dysthyroid optic neuropathy (DON).(5) In the chronic fibrotic phase, lid retraction, proptosis and restrictive strabismus are the most common findings. Patients with GO pose few diagnostic difficulties when these characteristic ocular findings occur concomitantly with the thyroid disease. However, when unilateral or inconclusive ocular features occur in the absence of objective evidence of thyroid dysfunction, GO can be difficult to diagnose.(6)

Among the ocular features, eyelid retraction plays a major role in the clinical diagnosis of the disease. According to Bartley and Gorman's diagnostic criteria (7), GO may be diagnosed when eyelid retraction occurs in association with exophthalmos, DON or extraocular muscle involvement. If eyelid retraction is absent, positive laboratory tests are required for diagnosis.

Affecting 4-8% of patients, DON has long been recognized as the most feared complication of GO.(8, 9) Although inflammatory (10-12) and ischemic mechanisms (13) have

been suggested, the most widely accepted explanation is mechanical compression of the optic nerve at the orbital apex by enlarged extraocular muscles.(14) Because DON involves a wide range of presenting symptoms and signs, diagnosis relies on several clinical features, including decreased visual acuity (VA), abnormal visual fields (VF), impaired color and brightness perception, delayed visual evoked potentials, afferent pupillary defects and edema or atrophy of the optic nerve head.(9) Patients with GO are often assumed to have DON when one of these features is present and no other cause of the defect is observed, but visual impairment in GO is not uncommonly related with other factors. (15) Hence, in GO patients, direct optic nerve function testing can yield misleading results which sometimes make it difficult to distinguish probable from definitive DON.

While the diagnosis of GO and DON rests mostly on clinical signs associated with laboratory tests suggestive of thyroid dysfunction and autoimmunity, imaging studies such as computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography (US) and color Doppler imaging (CDI) can also be extremely important in both diagnosis and clinical or surgical follow-up. Imaging studies can verify possible extraocular muscle involvement as part of the diagnostic workup and may help distinguish the early acute inflammatory stage from the fibrotic, inactive stage of the disease.(16) Finally, imaging studies of patients prone to develop DON make timely diagnosis and treatment of the condition possible, avoiding permanent visual loss.(17) The purpose of this paper was therefore to review imaging modalities that can be of help in the diagnosis and management of GO, with a special emphasis on the diagnosis of GO-related optic nerve dysfunction.

Imaging modalities in Graves' orbitopathy

Computed tomography (CT)

CT scan distinguish normal from abnormal structures of different tissue density based on differential X-ray absorption. Fat and water have low densities and hence appear black in contrast to denser muscles, optic nerve and very bright bony structures on CT. Acting as a “natural contrast medium”, the presence of orbital fat allows high spatial and density resolution of orbital structures.(18) Tissue differences inherent to the orbit obviate the need for intravenous contrast in many situations. After digital recording, data are converted via an arithmetic procedure into different greyscales. Compared to isodense tissues (e.g. the brain), tissues with high absorption values (e.g. bone) appear as hyperdense whereas tissues with low absorption values (e.g. water or fat) appear as hypodense.(4)

The introduction of spiral CT in the early 1990s represented a fundamental evolutionary step in the development and ongoing refinement of CT imaging techniques. Continuous scanning of anatomical regions within a short time frame yields compelling results and the technology has been shown to offer undisputable advantages with regard to lesion detection and isotropic spatial resolution.(19) Individual volume elements obtained from axial slices can be reformatted in any plane to produce coronal, sagittal, paraxial or parasagittal oblique images. In contrast to direct coronal scans, sagittal and coronal reformations avoid high spatial frequency artifacts from dental appliances and other metal implants. Multiplanar reformations make it possible to view a lesion in the optimal anatomic plane and determine its location relative to contiguous orbital, bone, sinus and central nervous system structures. The advent of multidetector computed

tomography (MDCT) has enhanced image quality and resolution through the simultaneous acquisition of multiple slices and faster gantry rotation.(20)

Magnetic Resonance Imaging (MRI)

Hydrogen nuclei with an odd number of nucleons (protons and neutrons) behave as small magnets or dipoles. Protons are ubiquitous and their resonance is the basis of MRI techniques. (21) Thus, MRI captures signals from free-moving protons in a given tissue as they return to their primary position in a high magnetic field after deflection by a frequency pulse. Bright signals are defined as hyperintensity and dim signals are defined as hypointensity. When an organ is placed in a magnetic field, there is a net alignment of protons. Radio-frequency excitation reverses the polarity of some of these hydrogen nuclei, raising their level of energy. When the excitation stops, the protons return to baseline polarity emitting a measurable amount of energy. This is called T1 relaxation (T1) and is best measured just after the end of the radio-frequency excitation. Radio-frequency excitation also initiates a uniform synchronous precession, or spin, among the protons. Following the excitation, the spinning subsides at different rates in different molecular environments. The energy emission measured from this event is called T2 relaxation time (T2).(4) T1 and T2 can be used to distinguish between tissue types with different proton density. T1-weighted (T1w) images may be used to evaluate anatomic structures, while T2-weighted (T2w) images provide useful information about tissue composition. Additionally, certain T1 or T2 weightings achieved by applying special prepulses can be used to distinguish water from fat.

Ultrasonography (US)

Grayscale US has been used in ophthalmology since the late 1950s. Standardized diagnostic US in eye diseases is performed using high frequencies (optimally 8 MHz) and small

wavelengths to visualize small ocular structures. Both transocular A-scan and B-scan echograms are performed. A-scans are used to assess tissue characteristics based upon reflected acoustic waves. This technique is particularly sensitive for indicating the thickening or thinning of muscles or differentiating underlying pathologies. Reflectivity in the extraocular muscles may change as a result of tissue edema and cellular infiltration.(4) B-scans make it easier to visualize orbital structures, especially for non-ultrasonographers. B-scans are very helpful in topographic evaluations and when determining whether individual recti muscles are enlarged.

The main advantages of orbital US are its low cost and the lack of ionizing radiation. In addition, in experienced hands a relatively short examination time is required to monitor anterior/midorbital therapeutic response. The main disadvantages are its high intra- and interobserver variability, the inability to adequately visualize the orbital apex and the poor quality of anatomic information on the bony orbital walls, compared to the information provided by CT and MRI.(18)

Color Doppler imaging (CDI)

CDI is an ultrasonic imaging modality which allows to assess blood flow in real-time on a grayscale B-mode background. The technique was first described in 1979 (22) and is well-tolerated and widely used as a noninvasive imaging technique in many medical specialties. More recently, CDI was introduced as an adjunct to clinical examination and cross-sectional imaging for evaluating a number of pathological conditions in the orbit. Although the topography of the orbital structures may to some extent be evaluated with grayscale US, CDI makes it possible to assess blood flow in the orbital vessels and to detect changes in the perfusion of orbital arteries and veins.(23)

CDI produces conventional grayscale US images along with information regarding the direction and velocity of the blood flow. The velocity data are superimposed on the grayscale image by assigning a color scale to them. (24) The indications for and uses of CDI in ophthalmology are still evolving but include mostly vascular disorders. CDI has been used to investigate changes in blood flow parameters in disorders such as anterior ischemic optic neuropathy, central artery occlusion, central retinal vein occlusion, glaucoma, diabetes mellitus, ocular ischemic syndrome, uveitis and endophthalmitis. In orbital abnormalities, CDI is well suited for the evaluation of cavernous-carotid fistula, orbital varix, orbital tumors, orbital cellulitis and orbital inflammatory conditions.(24, 25)

The major blood supply to the orbit is through the ophthalmic artery (OA) whereas the major venous drainage is through the superior ophthalmic vein (SOV) to the cavernous sinus. CDI is able to assess OA and its branches, such as the drainage veins (SOV) and the inferior ophthalmic vein. CDI assessment of patients with GO is of great importance as studies have shown that venous congestion plays a significant role in the pathogenesis of the disease.(26)

Imaging studies for diagnosing GO and defining disease activity

Imaging studies can be helpful in establishing the diagnosis of GO as they provide objective morphological findings of the orbital structures. Based on such studies (especially MRI and CT), it is possible to establish the degree of extraocular muscle and orbital fat enlargement, exclude coexisting orbital pathology, clarify a confusing clinical picture and make surgical planning.(12) CT scan with positive findings is included in many sets of diagnostic criteria for GO.(7, 27-30)

GO presents a rather unique imaging pattern. The extraocular muscles appear to be the primary area of orbital involvement. Despite attempts to establish normative measurements (31-34), the assessment of muscle enlargement is often subjective and requires comparison with the opposite orbit or prior qualitative experience. Patients with GO usually present symmetrical, multiple extraocular muscle enlargement in both orbits, although asymmetrical muscle involvement can occur. On the other hand, true unilateral orbital involvement is unusual, occurring in only 6 to 10% of patients.(35) The muscles most frequently affected are the medial and inferior recti (Figure 1).

In a series of 116 CT scans of a heterogeneous population of patients with GO in different stages of the disease, 85% displayed definitive enlargement of the extraocular muscles.(36) The inferior and the medial recti were involved in 77% and 75%, respectively, and were the most severely enlarged. The lateral (51%) and superior (50%) recti were involved less frequently and less severely. Nevertheless, a later study found similar levels of enlargement for the four major muscle groups.(32) In another CT scan study involving 349 thyroid patients, the inferior, medial, superior and lateral recti were enlarged in 43%, 38%, 29% and 16% of cases, respectively. Two or more muscles were enlarged in 70% of the patients with ocular involvement.(37)

Unlike patients with orbital myositis or idiopathic orbital inflammation, evidence of muscle involvement in GO is ordinarily limited to the nontendinous portion of the muscle. Furthermore, in GO the extraocular muscles appear to be enlarged in a fusiform fashion, with sharp borders.(38) However, atypical cases with tendon involvement and blurred muscle margins have been described.(31, 39-41)

In the evaluation of extraocular muscle characteristics in GO, CT and MRI are the preferred imaging procedures, although US may also be a useful. (42) In clinical practice, US may conveniently be used to measure extraocular muscles and exclude other diseases. Indeed, while some authors have used US to evaluate muscle size, the technique was found to be somewhat inaccurate and to add no new information to knowledge obtained from current CT and MRI studies.(37, 43, 44)

Although the extraocular muscles are described as the “shock organ” of GO (31), many studies suggest that expansion of the orbital fat compartment also represents a major component of the disease process.(45, 46) In GO, while some affected orbits are characterized by prominent extraocular muscle enlargement, others display mild or non-extraocular muscle involvement, occasionally with clearly increased adipose tissue volume. Imaging studies can distinctly show these clinical differences (Figure 2). Thus, orbital fat augmentation observed on CT is included in some reported diagnostic criteria for GO.(28, 47). The observation of exophthalmos in patients with abnormally increased orbital adipose tissue is suggestive of GO, but obesity and Cushing disease should also be considered.(48).

GO is associated with a wide spectrum of radiological findings in addition to extraocular muscle and fat tissue enlargement, as described in the literature.(36, 49, 50) CT findings may include bone changes, especially the lamina papyracea of the ethmoid with bowing resulting from muscle pressure. Lacrimal gland displacement and enlargement, exophthalmos, anterior soft tissue swelling and superior optic vein dilatation may also be observed in imaging studies, but these are unspecific findings which do not support the diagnosis of GO.(32, 51, 52)

CT is generally the preferred imaging modality for the diagnosis of patients with GO due to its ability to visualize bone and soft tissues in the orbit. CT also helps evaluate the orbital

walls, sinus and orbital elements in orbital decompression planning. Compared to MRI, CT is less expensive and faster to perform, but also less efficient in the evaluation of soft tissue changes. Furthermore, MRI can reveal details that may be of help in the assessment of disease activity.

In addition to their importance in the diagnosis of GO, imaging studies can help evaluate inflammatory disease activity. Sequential measurements of extraocular muscles on CT may be correlated to clinical activity; thus, muscular involvement occurs early in GO and subsides along with other clinical signs.⁽⁵³⁾ Nevertheless, studies assessing disease activity rely primarily on MRI due to its better performance in the evaluation in soft tissues.

MRI estimates disease based on the water content of the tissues. In GO, strong T2-weighted and fat-suppressed images, the so-called TIRM (turbo-inversion recovery-magnitude) and STIR (short-tau inversion recovery) sequences, have been described as useful in detecting extraocular muscle edema.⁽⁵⁴⁾ In order to differentiate active from inactive GO, inflammatory edema of the extraocular muscles must be distinguished from fibrous end-stage disease with fatty degeneration using T2 relaxation time, which is shorter for fibrous than for inflammatory tissue (Figure 3).⁽⁵⁵⁾ However, edema is not always correlated with disease activity since it can also be the result of both active inflammation and reduced venous outflow in patients with fibrotic disease. Indeed, some studies have shown that on T1w images, when gadolinium is combined with fat saturation techniques, it is possible to distinguish inflammatory edema from congestive venous outflow in burned out disease (Figure 4).^(55, 56) Non-fat-saturated T1w images are also useful in the detection of fatty muscle degeneration. These fatty or fibrotic muscle changes display no contrast enhancement on matched fat-saturated T1w images.

In the management of GO, it is of great importance to estimate disease activity when selecting patients most likely to respond to immunosuppressive treatment. Clinical activity scales, such as the clinical activity score (CAS) described and validated by Mourits and the Amsterdam Orbitopathy group (57) and the VISA classification described by Dolman and Rootman (58), can be very helpful in the assessment of disease activity. It would seem that the combination of MRI studies and clinical scores would improve diagnostic accuracy, but results have been conflicting. Thus, some researchers found no clear correlation between MRI findings and CAS indexes (54, 59, 60), perhaps due to the great variability of CAS scores among different observers or because only extraocular muscles, and no inflamed orbital fat, were assessed, while others reported significant positive correlations.(61) Despite the controversy, MRI seems to be useful to monitor response to treatment using measurements such as signal intensity (SI) and the signal intensity ratio (SIR).

US has also been proposed for evaluating disease activity. Prummel et al.(62) showed extraocular muscle reflectivity changes in the inflammatory phase of GO, suggesting US is a reliable tool for the determination of disease activity. In the active phase, extraocular muscles seem to have reduced internal reflectivity presumably due to edema, while they tend to show irregularly high reflectivity in end-stage disease due to fibrotic echogenic scar tissue. Nevertheless, not all studies have found a correlation between CAS and US reflectivity.(59, 63) Moreover, US is believed to provide less comprehensive information on extraocular muscles and inflammation than MRI. It should also be noted that adequate measurement of muscle reflectivity requires standardized A-wave US equipment and an experienced examiner.

CDI has also been used as a tool for diagnosing GO and assessing disease activity. A number of studies have compared orbital blood flow in patients with GO and controls (25, 64,

65) as well as in patients with different clinical forms of GO.(66) Benning et al.(64) found that, compared with controls, flow velocity in the right ophthalmic artery was markedly enhanced in subjects with clinically active GO. This finding was also reported by Alp et al.(25) and thus supports the assumption that orbital inflammation may increase orbital blood flow. Research in this field is promising: in fact, Monteiro et al.(26) recently compared CDI findings for orbits with the active form of the disease to findings for the same orbits after (mostly surgical) treatment and found a significant difference.

Finally, patients with GO may be diagnosed with octreotide scintigraphy (octreoscan). Octreotide is a somatostatine (SM) analogue labeled with indium, a substance which has been used to localize tumors with membrane receptors for SM. Based on the assumption that orbital lymphocytes express SM receptors during the active phase of GO, a high uptake of radiolabelled octreotide may be correlated with orbital inflammation and active disease.(67, 68) A positive orbital octreoscan could be useful in the assessment of disease activity in GO; nevertheless, the fact that the technique is expensive, non-specific and associated with a non-negligible radiation burden restricts its clinical application.(4)

Imaging studies for the diagnosis of dysthyroid optic neuropathy

Computed tomography (CT)

Several studies have indicated that a number of CT scan parameters can help raise suspicion of DON. Although increased orbital fat associated with axial proptosis leading to stretching of the optic nerve is in rare cases considered a possible pathogenic mechanism (69), the most important mechanism for developing optic neuropathy is orbital apical crowding by enlarged extraocular muscles.(9, 14, 17, 32, 52, 70-73) Since apical crowding on CT imaging is

strongly correlated with DON in GO, many CT studies have proposed indexes designed to objectively detect DON in a number of different ways.

In a pioneer study based on linear measurements of extraocular muscles and the bony orbit, Barrett (52) described a simple method of quantifying extraocular muscle impingement on the optic nerve space. Using a reformatted scan halfway between the posterior globe and the orbital apex, the vertical diameters of the superior rectus muscle/levator muscle complex (A) and inferior (B) rectus muscles and orbital height (C) were measured with a ruler along a horizontal line through the optic nerve. The vertical muscular index was expressed as the percentage of orbital height occupied by the superior rectus muscle/levator muscle complex and inferior rectus muscles ($[A+B/C] \times 100$) (Figure 5). In the same manner, the transverse dimensions of the medial, lateral rectus muscle and orbital width were measured and the horizontal muscle index was determined ($[D+E/F]$) (Figure 5). The greater of the two ratios was considered the muscle index. The study revealed that a muscle index of 67% or greater indicated compressive neuropathy and had a diagnostic sensitivity of 67%, although no patient with NOD had a muscle index under 50%. In a recent study using MDCT imaging, this linear index displayed the best combination for sensitivity and specificity (79%/72%) at a muscle index of 60% (71) When revisited by other authors, Barrett's index was found to have a satisfactory performance in the detection of DON.(17, 73)

Subjective assessment of apical crowding based on single coronal images, as described by Nugent et al.(32) and revisited by others (9, 17, 70, 73, 74), has also been shown to be a good predictor of DON. In these studies, a coronal image at the apex is subjectively graded in reference to the severity of muscle crowding. According to this method, effacement of the perineural fat is graded 0 (none), 1 (up to 25%), 2 (25-50%) or 3 (greater than 50%) (Figure

6).(32) Thus, Nugent et al. found severe apical orbital crowding (grade 3) in 12 of 18 orbits with DON, but only in 16 out of 124 orbits without DON.(32) Neigel et al. graded as moderate or severe crowding 79.2% of the orbits with DON and 12.9% of the orbits without DON.(9) Birchall et al. found severe apical crowding to be a good predictor of DON, with a sensitivity of 62% and a specificity of 91%.(74) A recent multicenter study found apical muscle crowding in 49 out of 56 orbits with DON.(70) In another study, severe optic nerve crowding was retrospectively noted in 80% of orbits (16 of 20) with optic neuropathy compared to 29% of orbits without DON (10 of 34). No orbits with optic neuropathy had less than grade-2 evidence of optic nerve crowding.(17) However, while it seems clear that Nugent's apical crowding score is useful for raising suspicion of DON, it does not provide a clear definition of the position along the orbit where the coronal plan is used to determine it, nor a clear differentiation between grade-1, 2 and 3 orbital crowding. More recently, objective quantification of apical orbital crowding based on square area measurements was shown to be a more efficient diagnostic tool than subjective quantification. In that study, the best-performing index was highly efficient at detecting DON, with a sensitivity of 91.7% and a specificity of 90.0%.(75)

Chan et al (73) highlighted the importance of evaluating not only extraocular muscle enlargement but also the role of the bony orbit and its usefulness as predictor of DON. The bony orbit capacity was quantified by using standardized orbital angles on axial scans. The study indicated that such measurements were independent predictors of DON and that narrower orbits are more susceptible to develop DON. The authors also calculated an index of orbital muscular crowding in combination with lateral and medial orbital wall angles with 73.3% sensitivity and 90% specificity.

Birchall et al.(74) found intracranial fat prolapse through the superior orbital fissure to be a predictor of DON, but later studies have not confirmed the usefulness of this parameter.(70, 73) Other CT features have been tested as indicators of DON, including lacrimal gland displacement, exophthalmos, superior optic vein dilatation and single muscle measurements, yielding conflicting and for the most part discouraging results.(9, 17, 32, 52, 74, 76)

Although linear or square measurements have proved helpful in diagnosing DON, the estimate of orbital apex crowding based on volumetric estimates of structures could potentially improve the ability to detect DON. In fact, Feldon et al.(14, 77) have used volumetric estimation of orbital content to investigate the risk of developing DON in GO. Previously, such measurements involved cumbersome calculations of extraocular muscles, but recent advances in CT using MDCT have made volumetric estimates of orbital structures readily available at a workstation.(78) In a recent study, orbital crowding indexes were, for the first time, calculated based on volumetric analysis of CT images. Orbital fat and muscle volume were estimated, based on different attenuations in Hounsfield Units, from measurements from the anterior orbital rim up to the optic foramen. Based on these measurements, two volumetric indexes of orbital muscle crowding were calculated: one based on axial scans of the entire orbit and another based on coronal scans of the orbital apex. Both indexes were efficient at predicting DON, especially the index limited to the orbital apex (92% sensitivity, 86% specificity).(79)

Magnetic Resonance Imaging (MRI)

Very few MRI studies have assessed DON directly. Dodds et al.(80) assessed DON in a high-resolution MRI study in which he compared three groups (control, GO with DON, and GO without DON) with regard to the diameter of the optic nerve in seven different positions from the eye ball to the pre-chiasmal region. The optic nerve diameter was significantly smaller in the

group with DON. However, the overall reduction was not substantial, with far too much overlap between controls and patients with DON. The authors admitted that, despite the observed reduction in optic nerve size in the DON group, neural compression could not be proven to be the pathogenic mechanism underlying nerve dysfunction, but found mechanical compression of the optic nerve to be the most plausible explanation. Alternatively, DON might be caused by vascular compression or by some other unidentified mechanism. The authors also observed reductions in optic nerve diameter in the absence of enlarged extraocular muscles, suggesting the compression results from increases in intraorbital pressure owing to increased fat volume.

Although CT is excellent for outlining bone details, MR imaging provides better soft tissue detail and is helpful for evaluating the extraocular muscles, optic nerve and fat. Therefore, further studies are necessary to better investigate the ability of MRI to detect DON, alone or in association with CT.

Ultrasonography and color Doppler imaging

In some studies, US has been used to estimate the presence of DON. One study suggested that US can detect DON-related enlargement of the subarachnoid space of the optic nerve, but apparently this is only rarely noted.(4) The evaluation of the venous flow can also be useful. Monteiro et al.(66) reported that patients with congestive orbitopathy and with predominantly myogenic fibrotic GO experience a significant reduction in SOV flow, matching reports by other authors(81) and supporting the notion that orbital congestion due to extraocular muscle enlargement can reduce orbital venous drainage. Since DON is known to be related to orbital apex crowding, the existence of severe venous stasis in the orbits possibly reflects a stage in its development. While both US and CDI can produce findings suggestive of DON, more systematic

studies separating congestive cases with DON from cases without DON are necessary to determine the actual usefulness of these methods.

Conclusions

While the diagnosis of GO and DON still relies heavily on clinical data, the last decades have seen outstanding developments in orbital imaging techniques. Important imaging studies have led to the emergence of new perspectives in diagnosis and treatment of GO, which constitute the main topic of this review.

As described above, CT remains the main imaging modality in Graves' disease. It may be used to establish the degree of extraocular muscle and orbital fat enlargement, to clarify a confusing clinical picture and to aid surgical planning. Furthermore, CT can be of great help in the detection of DON using linear, area or volumetric indexes of orbital apex crowding. However, it provides little information on disease activity, except through the observation of changes in sequential studies.

MRI can also be used to diagnose GO. However, its ability to raise suspicion of DON has still not been explored, perhaps due to the difficulty of estimating orbital bone volume and thereby determine the amount of orbital apex crowding. On the other hand, due to its greater ability to differentiate soft tissues, MRI has become a useful adjunct in imaging studies of GO patients, when GO-related muscle involvement needs to be differentiated from other orbital conditions. Furthermore, progressive technical refinements will probably further enhance its usefulness, especially in the assessment of GO activity upon diagnosis and during treatment.

US is a time-honored, very accessible and low-cost technique widely used to detect extraocular muscle enlargement. However, the lack of a more accurate evaluation of the orbital

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apex, compared to CT or MRI, has reduced its importance in the diagnosis and management of GO. In contrast, though still in its early developmental stage, color Doppler imaging may become useful in the management of GO: it is the technique that best evaluates orbital venous congestion, a possible contributing factor during the active congestive stage of GO.

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Figure Legends

- Figure 1.** Coronal CT scans in two distinct patients with Graves' Orbitopathy. **A:** shows a case with symmetric enlargement of the extraocular muscles in both orbits. **B:** shows a case with asymmetrical involvement of the extraocular muscles.
- Figure 2.** Axial CT scans in two distinct patients with Graves' Orbitopathy. **A:** shows a case with prominent enlargement of the medial and lateral recti muscles. **B:** shows a case with severe proptosis of both orbits with non extraocular muscle involvement and clearly fat tissue augmentation.
- Figure 3.** Coronal STIR MR image showing bright signal of the superior oblique muscles, inferior, medial and superior recti muscles in both orbits in a patient with active Graves' Orbitopathy.
- Figure 4.** Coronal T1-weighted MR images in a patient with active Graves' Orbitopathy. **A:** Image showing enlargement of extraocular muscles without fatty degeneration. **B:** Fat-suppressed and gadolinium-enhanced image shows bright signal of the inferior, medial and superior recti muscles.
- Figure 5.** Schematic representation of the method for calculating Barrett's muscle index. The vertical index was calculated by the sum of the vertical muscle diameter (A and B) divided by the height of the orbit (C). The horizontal index was calculated by dividing the sum of the horizontal muscle diameter (D and E) by the horizontal diameter of the orbit (F).
- Figure 6.** Coronal CT scan showing orbits with apical crowding by enlarged extraocular muscles. The right orbit presents effacement of the perineural fat up to 25% of the circumference (grade 1 in Nugent's score); the left orbit presents effacement of the perineural (grade 0).

Figure 1. Coronal CT scans in two distinct patients with Graves' Orbitopathy. A: shows a case with symmetric enlargement of the extraocular muscles in both orbits. B: shows a case with asymmetrical involvement of the extraocular muscles.
109x99mm (300 x 300 DPI)

Figure 2. Axial CT scans in two distinct patients with Graves' Orbitopathy. A: shows a case with prominent enlargement of the medial and lateral recti muscles. B: shows a case with severe proptosis of both orbits with non extraocular muscle involvement and clearly fat tissue augmentation.
109x134mm (300 x 300 DPI)

Figure 3. Coronal STIR MR image showing bright signal of the superior oblique muscles, inferior, medial and superior recti muscles in both orbits in a patient with active Graves' Orbitopathy.
109x59mm (300 x 300 DPI)

view Only

Figure 4. Coronal T1-weighted MR images in a patient with active Graves' Orbitopathy. A: Image showing enlargement of extraocular muscles without fatty degeneration. B: Fat-suppressed and gadolinium-enhanced image shows bright signal of the inferior, medial and superior recti muscles.
109x128mm (300 x 300 DPI)

Figure 5. Schematic representation of the method for calculating Barrett's muscle index. The vertical index was calculated by the sum of the vertical muscle diameter (A and B) divided by the height of the orbit (C). The horizontal index was calculated by dividing the sum of the horizontal muscle diameter (D and E) by the horizontal diameter of the orbit (F).
109x48mm (300 x 300 DPI)

Figure 6. Coronal CT scan showing orbits with apical crowding by enlarged extraocular muscles. The right orbit presents effacement of the perineural fat up to 25% of the circumference (grade 1 in Nugent's score); the left orbit presents effacement of the perineural (grade 0).
109x54mm (300 x 300 DPI)

4 METODOLOGIA

4.1 Desenho do estudo

Foi realizado um estudo observacional, transversal, descritivo e prospectivo, no qual foram incluídas órbitas de pacientes com OG com e sem NOD. O estudo seguiu os critérios da Declaração de Helsinki e obteve aprovação da comissão de ética para análise de projetos de pesquisa (CAPPesq) da diretoria clínica do Hospital das Clínicas e da Faculdade de Medicina da Universidade de São Paulo em 14 de dezembro de 2005 (protocolo de pesquisa n° 1152/05).

4.2 Pacientes

Noventa e três novos pacientes admitidos no serviço de órbita da clínica oftalmológica do Hospital das Clínicas de São Paulo, no período entre dezembro de 2005 e agosto de 2010, foram estudados. Consentimento livre e esclarecido foi obtido dos participantes do estudo. A OG foi diagnosticada de acordo com critérios previamente estabelecidos.⁽⁴²⁾

Todos os pacientes foram submetidos a um exame oftalmológico, incluindo medida da acuidade visual corrigida (tabela de Snellen), exame refracional dinâmico, inspeção das pálpebras, medidas da fenda palpebral, exoftamometria de Hertel,

medida da pressão intraocular utilizando o tonômetro de aplanção de Goldmann, biomicroscopia, exame das pupilas, fundoscopia e exame de campo visual.

Os exames de campo visual foram obtidos pela técnica automatizada e em alguns casos pela técnica manual. Para o exame de perimetria manual foi utilizado o perímetro de Goldmann (Haag-Streit AG, Berna, Suíça). Os estímulos V-4-e, I-4-e, I-3-e, I-2-e e I-1-e foram utilizados para desenhar os isópteros. Determinações cinéticas foram seguidas por apresentações estáticas do estímulo na área de 30° centrais do campo visual, a fim de pesquisar defeitos localizados. A campimetria computadorizada foi realizada com aparelho Humphrey *field analyser* 750 (Zeiss-Humphrey, Dublin, Califórnia) com a estratégia 24-2 SITA-*Standard*. Os pacientes fizeram o exame com correção óptica para perto e, para maior conforto, lhes foi fornecido apoio para os membros superiores. Na campimetria computadorizada, o exame foi considerado anormal quando três pontos adjacentes anormais ($P < 0,05$) ou dois pontos adjacentes com pelo menos um anormal ($P < 0,01$) eram observados.⁽⁴³⁾

Os seguintes critérios determinavam a exclusão dos pacientes examinados do estudo:

1. Idade menor que 20 anos;
2. Pouca colaboração na realização do exame de campimetria;
3. Erro refracional superior a 5 dioptrias esféricas;
4. Erro refracional superior a 3 dioptrias cilíndricas;
5. Exame de campo visual não confiável. Na perimetria computadorizada, o exame de campo visual era considerado não confiável quando a perda de fixação, os falso-positivos ou os falso-negativos superavam o valor de 25%;

6. Anomalias de disco óptico, sinais clínicos de neuropatia glaucomatosa ou outras neuropatias que não a NOD;
7. História pregressa de cirurgia orbitária ou de estrabismo;
8. Outras causas de baixa visual, como catarata, anormalidades da transparência corneana ou doenças retinianas.

Foram consideradas para o estudo apenas as órbitas com OG e função visual bem definida tanto para a presença como para a ausência de NOD. O critério para o diagnóstico da NOD foi definido pela presença de defeito pupilar aferente relativo e de defeito no campo visual, diagnosticado na campimetria computadorizada ou manual, associados ou não a um déficit da acuidade visual corrigida e não causada por opacidades de meio. No caso de olhos com acuidade visual normal e campo visual com defeito no exame computadorizado, um novo exame ou um exame com a campimetria manual de Goldmann era realizado para confirmar a presença de defeito e excluir achados falso-positivos. Consequentemente, olhos com acuidade visual corrigida normal que não apresentassem reprodutibilidade em exames seguidos a presença de defeito de campo visual foram excluídos do estudo.

4.3 Tomografia computadorizada

Os pacientes foram submetidos a tomografia computadorizada de multidetectores (CTMD) (Brilliance 16, Philips Medical Systems, Holanda) sem sedação e sem o uso de contraste endovenoso dentro de um período de até duas

semanas do exame oftalmológico. As imagens da tomografia computadorizada foram obtidas por meio de cortes axiais contínuos do paciente deitado em decúbito dorsal e com a cabeça posicionada paralela ao plano de Frankfurt. Os pacientes eram instruídos a manterem seus olhos fechados e estáticos na posição primária do olhar. Os parâmetros de aquisição foram: 120 Kv, 200 mAs, detector com configuração 16x0,75 mm, com espessura de corte de 1,5 mm e 0,7 de incremento.

As imagens foram posteriormente processadas na estação de trabalho do próprio tomógrafo e avaliadas por um único radiologista, que não tinha conhecimento da presença ou ausência da NOD. A seguir, estão descritas as medidas e os índices calculados neste estudo.

4.4 Cálculo do índice de preenchimento muscular do ápice orbitário a partir medidas lineares

Utilizamos um método previamente descrito por Barrett e colaboradores ⁽³²⁾ para calcular um índice muscular capaz de quantificar o grau de preenchimento orbitário e compressão do nervo óptico. As medidas musculares foram realizadas em um corte coronal reformado exatamente no ponto médio do nervo óptico intraorbitário de cada órbita. As dimensões transversais dos músculos reto medial (A), reto lateral (B) e diâmetro orbitário (C) foram determinadas sobre uma linha horizontal que passava pelo nervo óptico. O índice muscular horizontal (IMH) foi calculado como a porcentagem do diâmetro no plano horizontal dos músculos retos

medial e lateral segundo a fórmula, $IM\ horizontal = \{(A+B)/C\} \times 100$. O índice muscular vertical foi calculado de modo semelhante, porém baseado em uma linha vertical sobre o nervo óptico. Nessa linha o complexo muscular reto superior/elevador da pálpebra (D), o músculo reto inferior (E) e a altura orbitária (F) foram determinados e o índice calculado conforme a equação $\{(D+E)/F\} \times 100$. O maior desses índices foi considerado o índice muscular de Barrett e utilizado para análise e comparação entre os grupos (Figura 1).

Figura 1. Representação esquemática do método de cálculo do índice de preenchimento muscular do ápice orbitário de Barrett. O índice muscular (IM) horizontal é calculado pela soma dos diâmetros horizontais dos músculos reto medial e lateral (A e B) dividida pela largura orbitária (C). O IM vertical é calculado pela soma dos diâmetros dos músculos complexo reto superior/elevador da pálpebra e reto inferior (D e E) pela altura da órbita (F). O maior destes índices é considerado o IM de Barrett

4.5 Cálculo do índice subjetivo de Nugent de preenchimento muscular do ápice orbitário

De acordo com um método previamente descrito por Nugent e colaboradores,⁽³⁸⁾ uma escala de 0 a 3 foi utilizada para categorizar o grau do preenchimento muscular e compressão do nervo óptico em um corte coronal reformado no ponto médio do nervo óptico intraorbitário. Essa escala é baseada na observação da circunferência do nervo óptico, em que o grau 0 (Figura 2) significa que não ocorre nenhuma obliteração por músculo extra-ocular da circunferência. No grau 1 (leve), entre 1 a 25% da circunferência do nervo óptico é obliterada por músculos. O grau 2 (moderado) é definido por uma obliteração de 25 a 50% da circunferência (Figura 2) enquanto no grau 3 (grave) a obliteração é de mais de 50%.

Figura 2. Corte coronal de ápice orbitário de TC de paciente com OG assimétrica. **A.** Na órbita direita observa-se obliteração da circunferência do nervo óptico compatível ao grau 2 na escala de Nugent. **B.** Na órbita esquerda não é observado obliteração da circunferência do nervo compatível ao grau 0 na escala de Nugent

4.6 Identificação de herniação de gordura pela fissura orbitária superior

Com um método descrito por Birchall e colaboradores,⁽³⁹⁾ identificamos em cada órbita do estudo a presença ou não de herniação de gordura pela fissura orbitária superior.

Em um corte axial das órbitas paralelo ao plano infraorbitomeatal, identificamos a fissura orbitária superior definida por uma linha entre a borda anterior do sulco no corpo do esfenóide formado pela porção intracavernosa terminal da artéria carótida interna e o ponto mais medial da borda interna da asa menor do esfenóide. A herniação de gordura intracraniana era considerada positiva caso a gordura orbitária fosse observada além de 2 mm dessa linha desenhada (Figura 3).

Figura 3. Cortes axiais de TC de pacientes com OG. **A.** Paciente com NOD bilateral e ausência de herniação de gordura pela fissura orbitária superior. **B.** Paciente sem NOD em ambas órbitas e presença de herniação de gordura pela fissura orbitária bilateralmente. Em **A** e **B**, a localização da fissura orbitária superior são demonstradas por linhas tracejadas

4.7 Cálculo do índice de preenchimento muscular do ápice orbitário a partir de medidas de área

Com um método inédito quantificamos com medidas de área o preenchimento muscular em três cortes coronais distintos do ápice orbitário.

A partir de um planejamento em uma imagem axial das órbitas do paciente, em um plano paralelo plano infraorbitomeatal e que incluía o nervo óptico, cortes coronais contínuos de 1 mm de espessura foram obtidos desde uma linha interzigomática até o ápice orbitário. Dentre esses cortes coronais, os cortes a 12, 18 e 24 mm foram definidos como alvo do estudo (Figura 4).

Figura 4. Representação esquemática do estudo com a TC. **(Esquerda)** Corte axial com os detalhes do planejamento de cortes coronais contínuos a partir da linha interzigomática. **(Direita)** Imagens coronais reformadas a 12, 18, e 24mm a partir da linha interzigomática

Com uma técnica baseada em limiares de unidades Hounsfield (UH), de um programa da própria estação de trabalho do tomógrafo, foram calculados os volumes das partes moles e do continente total da órbita. Como cada corte coronal adquirido

apresentava 1 mm de espessura, o cálculo volumétrico resultante corresponderia ao da área. Diferentes níveis (WL) e abertura (WW) de janela de UH foram predeterminados a fim de mensurar as partes moles (que incluem principalmente músculos, nervos e vasos) e o continente total da órbita. Os limiares estabelecidos foram para partes moles de +40/+100 (WL/WW) e para o conteúdo total orbitário de +10/+300 (WL/WW). Nas imagens coronais estudadas a região de interesse para tais medidas foi determinada com uma linha sobre os limites de cada órbita (Figura 5). Dessa forma, o programa foi capaz de calcular o preenchimento muscular em relação ao continente ósseo da órbita em cada corte coronal estudado.

Figura 5. (Esquerda) Exemplo de corte coronal reformado a 18mm da linha intezigomática. Na região delimitada por um linha circundando os limites ósseos, o continente orbitário foi calculado automaticamente baseado em limiares de UH (a direita, abaixo). Na mesma região a área dos músculos também foi calculada baseada em limiares de UH (a direita, acima). O índice de área de preenchimento muscular foi calculado pela razão entre a área muscular sobre a área continente total. Os limiares de UH utilizados para os cálculos de área excluía o tecido ósseo

4.8 Cálculo do índice de preenchimento muscular da órbita a partir de medidas de área

Dois índices volumétricos foram calculados, o primeiro baseado em medidas das estruturas orbitárias a partir de cortes axiais de todo o continente orbitário (do ápice à rima orbitária anterior) e um segundo baseado em medidas das estruturas orbitárias a partir de cortes coronais da órbita a partir de um ponto médio do segmento orbitário do nervo óptico até o limite anterior do canal óptico.

4.8.1 Cálculo do índice de preenchimento muscular da órbita a partir de medidas de volume em cortes axiais

Nessas medidas foram analisados cortes axiais contínuos. Os diferentes tecidos foram codificados em cores de acordo com suas respectivas atenuações em UH. Diferentes níveis (WL) e aberturas (WW) de janela de UH foram determinados a fim de separar automaticamente as partes moles (compostas por músculos, nervos e vasos) da gordura orbitária. Os limites estabelecidos foram, para partes moles, de 40/100 (WL/WW) e, para a gordura orbitária, de -160/-230 (WL/WW). Para delimitar a região de interesse a ser medida, em cada corte axial foi traçada uma linha nos limites orbitários (Figura 6). O limite anterior foi delineado por uma linha reta entre a rima orbitária temporal e a rima orbitária medial. Essa delimitação iniciou-se superiormente no primeiro corte tomográfico contendo a órbita e seguiu descendo continuamente, corte a corte, até que toda órbita fosse incluída. Os volumes dos tecidos contidos na região delimitada foram então estimados automaticamente pelo programa da estação

de trabalho (Figura 6). O índice volumétrico da órbita foi calculado pela razão entre o volume medido de partes moles sobre o volume da gordura orbitária.

Figura 6. A, B e C. Exemplos da delimitação da região de interesse, da sequência de cortes axiais, da qual as medidas de volume total foram calculadas. D. Representação do resultado da medida do volume total de partes moles da órbita (essencialmente músculos extra-oculares). E. Representação do resultado da medida de gordura orbitária. O índice volumétrico de preenchimento muscular da órbita foi calculado pela razão do volume muscular sobre o volume de gordura orbitária

4.8.2 Cálculo do índice de preenchimento muscular do ápice orbitário a partir de medidas de volume em cortes coronais coronais

A partir da imagem axial adquirida, cortes coronais de um milímetro de espessura foram reformatados entre a linha interzigomática e o ápice orbitário. O cálculo volumétrico incluiu apenas os cortes coronais da região posterior da órbita, a partir do ponto médio da porção orbitária do nervo óptico até, posteriormente, a

entrada do canal óptico (Figura 7). A gordura orbitária e as partes moles foram codificadas em cores com os mesmos parâmetros utilizados para as medidas volumétricas axiais. Para cada plano coronal predefinido a região de interesse foi definida por uma linha traçada sobre os limites ósseos da órbita. Os volumes dos tecidos contidos na região delimitada foram também estimados automaticamente pelo programa da estação de trabalho (Figura 8). O índice volumétrico do ápice orbitário foi calculado pela razão entre o volume medido de partes moles sobre o volume da gordura orbitária.

Figura 7. Detalhes do planejamento, a partir da imagem axial adquirida, dos cortes coronais a serem reformados entre a linha interzigomática e o ápice orbitário. As duas linhas limitantes da seta indicam os cortes coronais da região posterior da órbita de onde foram calculados o índice de volume de preenchimento do ápice orbitário. As duas linhas representam o ponto médio da porção orbitária do nervo óptico e, posteriormente, a entrada do canal óptico

Figura 8. A, B e C. Exemplos da delimitação da área de interesse, realizada nos cortes coronais do ápice orbitário reformados dos quais as medidas de volume apical foram calculadas. **D.** Representação do resultado da medida do volume apical das partes moles (essencialmente músculos extra-oculares). **E.** Representação do resultado da medida de gordura no ápice orbitário. O índice volumétrico de preenchimento muscular do ápice da órbita foi calculado pela razão do volume muscular sobre o volume de gordura orbitária apical

4.9 Estimativa de confiabilidade das medidas realizadas

Procuramos avaliar a confiabilidade das medidas de área e volumétricas realizadas. Para isso, o mesmo radiologista repetiu suas medidas em 26 órbitas selecionadas ao acaso, aproximadamente 8 meses após as medidas originais. Em outra ocasião, um segundo radiologista também realizou as mesmas medidas nesse grupo de órbitas, ambos sem o conhecimento da presença ou ausência da NOD.

Assim, foram calculados os coeficientes de correlação intraclass (ICC, do inglês *intraclass correlation coefficient*) para os índices de área e de volume entre o mesmo observador e entre dois observadores diferentes.

5 RESULTADOS

5.1 Descrição Resultados

Os resultados desta tese foram objetos de três publicações.⁽⁴⁴⁻⁴⁶⁾ O primeiro trabalho⁽⁴⁴⁾ avaliou, com a TC de multidetectores, a habilidade diagnóstica do índice muscular de medidas lineares, descrito primeiramente por Barrett e colaboradores,⁽³²⁾ na detecção da NOD. O segundo,⁽⁴⁵⁾ descreveu o cálculo dos três índices de preenchimento muscular orbitário e seus respectivos desempenhos diagnósticos comparados aos desempenhos do índice subjetivo de Nugent e da herniação de gordura. Nesse artigo também é descrita uma correlação entre os índices de área com a gravidade do defeito de campo visual dos pacientes com NOD. No terceiro artigo,⁽⁴⁶⁾ foram descritos e relatados os resultados da habilidade, em detectar NOD, dos dois índices volumétricos desenvolvidos em nosso estudo.

5.2 Artigo de medidas lineares

CLINICS 2008;63:301-6

CLINICAL SCIENCE

DIAGNOSTIC ABILITY OF BARRETT'S INDEX TO DETECT DYSTHYROID OPTIC NEUROPATHY USING MULTIDETECTOR COMPUTED TOMOGRAPHY

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OBJECTIVES: The objective of this study was to evaluate the ability of a muscular index (Barrett's Index), calculated with multidetector computed tomography, to detect **dysthyroid optic neuropathy** in patients with Graves' orbitopathy.

METHODS: Thirty-six patients with Graves' orbitopathy were prospectively studied and submitted to neuro-ophthalmic evaluation and multidetector computed tomography scans of the orbits. Orbits were divided into two groups: those with and without dysthyroid optic neuropathy. Barrett's index was calculated as the percentage of the orbit occupied by muscles. Sensitivity and specificity were determined for several index values.

RESULTS: Sixty-four orbits (19 with and 45 without dysthyroid optic neuropathy) met the inclusion criteria for the study. The mean Barrett's index values ($\pm$ SD) were $64.47\% \pm 6.06\%$ and $49.44\% \pm 10.94\%$ in the groups with and without dysthyroid optic neuropathy, respectively ($p < 0.001$). Barrett's index sensitivity ranged from 32% to 100%, and Barrett's index specificity ranged from 24% to 100%. The best combination of sensitivity and specificity was 79%/72% for BI=60% (odds ratio: 9.2).

CONCLUSIONS: Barrett's Index is a useful indicator of dysthyroid optic neuropathy and may contribute to early diagnosis and treatment. Patients with a Barrett's index $>60\%$ should be carefully examined and followed for the development of dysthyroid optic neuropathy.

KEYWORDS: Dysthyroid Optic Neuropathy. Multidetector computed tomography. Graves' Orbitopathy. Visual loss. Thyroid eye disease.

INTRODUCTION

Optic nerve dysfunction is a debilitating complication of Graves' orbitopathy (GO) occurring in 5-8.6% of patients,¹ and it is almost always a result of compression of the optic nerve at the orbital apex caused by enlarged extraocular muscles. Symptoms and signs of dysthyroid optic neuropathy (DON) may include decreased visual acuity (VA), abnormal

visual fields (VF), altered color and brightness perception, afferent pupillary defects, and edema or atrophy of the optic nerve head.¹ When the majority of these symptoms and signs are present, the diagnosis of DON is straightforward. It is, however, much more difficult to establish when changes in VA are subtle since such changes may be related to a number of other factors, including decreased corneal transparency due to exposure keratopathy.⁶ Furthermore, many tests for optic nerve dysfunction, such as VA, color and brightness perception and VF, especially when performed with standard automated perimetry (SAP), require full cooperation of an alert and motivated patient. Also, such tests will not infrequently render false positive results, particularly in patients with congestive GO, leading to diagnostic confusion. Objective tests capable

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of rapidly and accurately identifying patients prone to DON development are therefore highly desirable.

Computerized tomography (CT) studies in patients with DON often reveal enlargement of extraocular muscles at the orbital apex, and several authors have correlated the degree of apical crowding on CT scans with optic neuropathy in an attempt to raise suspicion of DON and facilitate its diagnosis.³⁻⁵ In 1988, Barrett et al.⁵ reported findings for a muscular index for CT expected to reflect extraocular muscle impingement of the optic nerve in patients with GO. The authors calculated the percentage of orbital width occupied by muscles (muscular index) from coronal and axial cuts halfway between the posterior aspect of the globe and the apex of the orbit. A muscular index of 67% or greater was reported to be indicative of compressive optic neuropathy.⁵ Nevertheless, the difficulties in obtaining perfectly oriented coronal cuts and in defining the exact position of the coronal cut along the length of the orbit make the technique inappropriate for routine use.

The introduction of multidetector computed tomography (MDCT) has resulted in significantly increased scanning speed and reduction of artifacts and errors in the evaluation of measurements of orbital contents, as the images may be reformatted in any plane with high resolution.⁶ Calculating structure indices and volumes is relatively simple and may be performed at a workstation connected to the equipment. Thus, the purpose of this prospective study was to evaluate the value of Barrett's index (BI) used in combination with MDCT as a predictor of DON in patients with GO.

MATERIAL AND METHODS

Between July 2005 and June 2007, 36 patients with GO were prospectively studied. GO was diagnosed in accordance with previously reported criteria.⁷ The study followed the principles of the Declaration of Helsinki, and approval was granted by the Institutional Review Board Ethics Committee. All patients underwent a complete neuro-ophthalmic examination, including best-corrected VA, applanation tonometry, pupillary reactions, extraocular motility evaluation, slit lamp examination, evaluation of eyelid and soft tissue inflammation, measurement of the lid fissure, Hertel exophthalmometry, fundoscopy, and VF evaluation.

VF was performed using manual perimetry and standard automated perimetry (SAP). Manual VF testing was performed using the Goldmann perimeter (GP) (Haag-Streit AG, Bern, Switzerland). The V-4-e, I-4-e, I-3-e, I-2-e and I-1-e stimuli were used to draw the isopters. Kinetic determinations were followed by static presentation of the stimuli particularly in the central 30-degree area, in order

to search for localized defects. SAP was performed with a Humphrey field analyzer 750 (Zeiss-Humphrey, Dublin, CA) using a 4-mm² Goldmann size III stimulus (0.43°) on a dim background (31.5 apostilb). The central field was measured by a threshold 24-2 test program that presents stimuli on a 6°-spaced grid encompassing the central 21° of the VF (24-2 SITA Standard test). The patients' appropriate near correction was used. Rest breaks were allowed when requested. To qualify as an abnormal VF on SAP, three adjacent abnormal points at $P < 0.05$ or two adjacent points with one abnormal point at $P < 0.01$ were required.⁸

Both orbits of each patient were scanned on a 16-slice MDCT scanner (Brilliance 16; Philips Medical Systems, Nederland B.V., the Netherlands) without the use of sedation or intravenous contrast. Scanning was performed with the patients' eyes closed and immobile. The MDCT scan parameters were: Kv = 120; mAs = 200; detector configuration = 16 x 0.75 mm; slice thickness = 1.5 mm; image spacing = 0.7 mm. We used the method described by Barrett et al.⁵ to generate a muscular index capable of quantifying extraocular muscle impingement on the optic nerve. A reformatted coronal scan halfway between the posterior globe and the orbital apex was used to calculate the muscular index. The transverse dimensions of the medial rectus muscle (A), the lateral rectus muscle (B), and the orbital width (C) were measured along a horizontal line through the optic nerve. The horizontal muscular index was calculated as the percentage of orbital width occupied by the lateral and medial rectus muscles $[(A+B/C).100]$ (Figure 1). The vertical muscle index was based on the vertical dimensions of the superior rectus/levator muscle complex (D), the inferior rectus muscle (E), and the orbital height (F) $[(D+E/F).100]$ (Figure 1). The larger value was considered the muscular index, corresponding to the Barrett Index (BI), and was used in subsequent data analysis.⁵ Measurements were made by an examiner that was not aware of the presence or absence of optic neuropathy.

Figure 1 - Schematic representation of the method for calculating Barrett's Index. The vertical index is calculated by the sum of the vertical muscle diameters (A and B) divided by the vertical dimension of the orbit (C). The horizontal index is calculated by dividing the sum of the horizontal muscle diameters (D and E) by the horizontal diameter of the orbit (F).

Sixty-four of the 72 orbits scanned were selected for the study. Orbits of eyes with GO and visual function data clearly indicating the presence or absence of active DON were eligible. The diagnostic criteria for DON were the presence of a relative afferent pupillary defect and the presence of a confirmed VF defect on SAP or GP associated or not with diminished best-corrected VA not caused by changes in transparency. When VA was normal and VF abnormalities were present on SAP, a repeat examination using SAP or GP was performed to rule out false positive responses. Thus, only eyes with confirmed VF defects were included in the analysis. Eyes with normal VA and nonreproducible VF abnormalities upon repeat examinations were excluded. Patients with ocular or optic nerve diseases that prevented the correct diagnosis of DON were also excluded. All patients with DON had an active disease, but less than four weeks of onset of visual disturbance and clinical signs of orbital congestive disease.

The sensitivity and specificity of BI for identifying eyes with DON was calculated in the conventional manner. A criterion with a high specificity, if positive, "rules in" the disease, and a test with a high sensitivity, if negative, "rules out" the disease.⁹ After carefully determining the presence or absence of DON, we calculated the sensitivity and specificity (with 95% confidence interval) for a number of pre-defined criteria for BI index values, including 40%, 50%, 60%, 67%, and 70%. The odds ratio for having DON was calculated for each of these values.

We used an unpaired t-test for comparisons between groups of orbits with and without DON and Fisher's exact test for evaluating the significance of sensitivity and specificity values. Adherence to normal distribution was assessed using the Shapiro-Wilk test. *P* values of less than 0.05 were considered significant.

RESULTS

Sixty-four orbits from 36 patients with GO were included in the analysis. Nineteen of these were from 12 patients (7 women and 5 men; mean age $\pm$ SD: 53.3 ± 10.4 years) who met the diagnostic criteria for DON. Seven patients had bilateral DON, and both orbits were included in the study. Five patients had only one orbit included in the group of DON; in two patients, the contralateral eye did not meet the criteria for DON; two patients had the contralateral eye excluded, since the presence or absence of DON could not be clearly determined; one patient had a history of central retinal artery occlusion unrelated to GO, which led to our exclusion of the contralateral eye. Forty-five orbits were affected with GO but not with DON; two of these were from patients with DON in the contralateral eye, while 43 were

from 24 patients (17 women and 7 men; mean age $\pm$ SD: 45.5 ± 15.2 years) with DON absent in both eyes. Five orbits in this group were excluded from the study: in three, the diagnosis of GO could not be established (unilateral GO); in one the eye was deviated in an extreme upward position, and therefore it was not possible to determine either the presence or absence of DON; and in one an old orbital fracture was observed.

Of the 19 orbits of eyes with DON, VA was 1.0 in 11, 0.9 in 4, 0.8 in 3 and 0.6 in one. The mean ($\pm$ SD) of SAP mean deviation was -7.48 ± 5.26 dB. Results from the glaucoma hemifield test were outside the normal range in 16 eyes and borderline in three. Exophthalmometry measurements in affected eyes ranged from 19 to 30 mm (mean $\pm$ SD: 24.66 ± 3.08 mm). Restrictive myopathy was present in all orbits with DON. Fundoscopic examination revealed optic disc edema in a single eye and no abnormalities in the remainder of the eyes. In the group without DON, VA was 1.0 in all eyes and exophthalmometry findings ranged from 20.0 to 28.0 mm (mean $\pm$ SD: 23.2 ± 2.1).

The mean BI $\pm$ SD for the groups with and without DON was $62.67\% \pm 8.14\%$ and $49.44\% \pm 10.94\%$, respectively ($p < 0.001$). Table 1 shows the relative frequency of orbits calculated with BI values of 40%, 50%, 60%, 67%, and 70% in the 64 orbits studied. Table 2 summarizes the sensitivity and specificity for the respective BI values. The sensitivity ranged from 32% to 100%, and the specificity ranged from 24% to 100%. The odds ratio was statistically significant for all values of BI values tested (Table 2). The best combination of sensitivity/specificity was 79%/72% for BI=60%, yielding an odds ratio of 9.2.

Table 1 - Relative frequency of orbits according to Barrett's Index, in 64 orbits with Graves' Orbitopathy (GO) with and without dysthyroid optic neuropathy (DON)

Barrett Index	GO with DON (n = 19)	GO without DON (n = 45)
40%	19 (100.0%)	34 (75.6%)
50%	19 (100.0%)	23 (51.1%)
60%	15 (78.9%)	13 (28.9%)
67%	8 (38.1%)	2 (4.4%)
70%	6 (28.6%)	0 (0%)

DISCUSSION

DON requires prompt diagnosis and treatment in order to prevent permanent damage to the visual function. Although DON can most often be diagnosed on clinical grounds based on visual function assessment, the presence of an afferent

Table 2 - The sensitivity, specificity and odds ratios with confidence intervals (CI) of several levels of Barrett's index for the diagnosis of 19 orbits with dysthyroid optic neuropathy and of 45 orbits of patients with Graves' Orbitopathy without dysthyroid optic neuropathy

Barrett's Index	Sensitivity (95% CI)	Specificity (95% CI)	Odds Ratio	P*
40%	1.0 (0.87-1.00)	0.24 (0.19-0.24)	Inf (1.51- Inf)	<i>0.025</i>
50%	1.0 (0.86-1.00)	0.49 (0.43-0.49)	Inf (4.49- Inf)	<i>< 0.001</i>
60%	0.79 (0.61-0.91)	0.72 (0.64-0.76)	9.2 (2.66-31.57)	<i>< 0.001</i>
67%	0.42 (0.27-0.49)	0.96 (0.89-0.99)	15.6 (3.19-73.97)	<i>0.001</i>
70%	0.32 (0.20-0.32)	1.0 (0.95-1.00)	Inf (4.95- Inf)	<i>< 0.001</i>

* Fisher's exact test. Significant values are in italics. Inf = infinity.

pupillary defect and fundoscopic abnormalities such as disc edema and choroidal folds, the diagnosis of DON can be difficult in many cases. The uncertainty in the diagnosis occurs mainly in non-cooperative patients or those who have difficulties in performing psychophysical tests such as SAP, which is particularly common in anxious patients with marked proptosis, lid retraction, and profuse tearing. Therefore, additional objective data such as imaging findings can be very helpful in the diagnosis.

Although inflammatory and vascular mechanisms have also been suggested, the most widely accepted mechanism of optic neuropathy suggests that pathologically enlarged extraocular muscles compress the optic nerve at the orbital apex. In fact, several authors have documented the relationship between DON and the size of the extraocular muscles as measured by CT.^{2,5,10-14} Other imaging features reflecting an increased volume of orbital contents, such as proptosis and apical crowding, have also been shown to be more common in patients with optic neuropathy.^{1,4,14} Birchall et al.¹⁵ suggested that CT evidence of fat herniating through the superior orbital fissure would be a useful indicator of DON. However, in recent reports by McKeag et al.,¹³ they observed this condition in only 40 of 94 eyes with DON, suggesting that it would have a low sensitivity as an indicator of DON. A gradation of apical crowding has been described by Nugent et al.⁴ These authors found apical crowding greater than 50% to be a useful indicator of DON, with a sensitivity of 66% and a specificity of 87%. McKeag et al.¹⁶ confirmed the usefulness of this indicator in a report of apical crowding greater than 50% in 78 of 98 eyes with DON. However, it should be noted that measuring apical crowding or the muscle occupation at the orbital apex is often a cumbersome task, since the muscle limits can be difficult to identify. Extraocular muscles, the superior orbital vein, and the optic nerve are frequently indistinct at the orbital apex even when high resolution CT is used.

Barrett et al.⁵ described what is probably the easiest and most reproducible method for correlating the degree of extraocular muscle enlargement with the development of DON: a muscular index calculated as the percentage of orbital width occupied by vertical and horizontal muscles in relation to orbital dimensions

as measured from the midpoint between the globe and the orbital apex. In a retrospective study, the authors concluded that a muscular index of 67%, as encountered in 12 of 49 orbits evaluated, would be virtually diagnostic of DON. Recently, in another retrospective study evaluating an index of 67%, Giaconi et al.¹¹ found that 55% of orbits with DON and six out of 34 orbits without DON met the criterion. All 20 orbits affected with DON presented a muscular index greater than 50%. In another retrospective study, Birchall et al.¹⁵ reported a sensitivity of 50% and a specificity of 73% for BI of 50%. These authors observed that only one of the 17 orbits with DON had BI of 67%, a result very different from those observed by Barrett et al.,⁵ probably as a result of the inclusion of milder cases of DON.

To our knowledge, this is the first prospective study using MDCT to investigate the sensitivity and specificity of BI. Since MDCT can achieve very accurate reformations in the coronal plane, with a clear definition of the position along the orbit, we believe that the study shows a significant improvement in quality and reproducibility, compared to previous reports. Furthermore, in our study patients were carefully and prospectively evaluated for the presence or absence of DON. Our results indicate that if a percentage of 67% is required for diagnosis, as suggested by Barrett et al.,⁵ DON would be identified in only 8 out of 19 affected orbits. Moreover, two orbits without DON met the criterion, despite careful evaluation with SAP indicating absence of VF abnormalities. Thus, a muscular index of 67% presented a sensitivity of only 42% and a specificity of 96%. In our study, when lower values of BI were tested, we observed a significant increase in sensitivity with a corresponding decrease in specificity. For example, when BI was 40%, the sensitivity was 100% and the specificity, 24%; with BI = 50%, the sensitivity was 100% and the specificity, 49%; with BI = 60%, the sensitivity was 79% and the specificity, 72%. Finally, for higher BI values, such as 70%, we have found a sensitivity of 32% and a specificity of 100%. The best combination for sensitivity/specificity was therefore observed with BI = 60%. With this index, the odds ratio for the presence of DON was 9.2 (95% confidence interval; 2.66 - 31.57).

Our study indicates a BI of 67% is neither required for nor an

absolute indicator of the presence of DON. However, it is important to consider that BI could also vary depending on the severity of the neuropathy. For example, Guy et al.¹⁷ considered DON to be severe when visual acuity was equal to or worse than 20/80. Because we included patients with milder forms of DON, it is understandable that some of the subjects presented lower BI values. Furthermore, because BI is measured on the orbit halfway between the globe and the optic canal, it is likely that diagnoses in some patients with predominantly apical muscle enlargement are missed. Finally, it is important to point out that, although extraocular muscle enlargement is the most likely mechanism for the development of visual loss in DON, unusual cases of DON without extraocular muscle enlargement have been reported.¹⁸

Despite these limitations, we believe BI can be helpful when screening for DON because it is easily calculated for patients with GO submitted to MDCT. Our findings indicate that patients with a muscular index greater than 60% should be carefully examined for the presence of DON. Although high index values may be found in some patients with GO and normal visual function, the great majority of cases will have values associated with DON, and thus this assessment may contribute to early diagnosis and treatment.

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5.3 Artigo de medidas de área

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ORIGINAL RESEARCH

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Quantification of Orbital Apex Crowding for Screening of Dysthyroid Optic Neuropathy Using Multidetector CT

BACKGROUND AND PURPOSE: DON, a serious complication of GO, is frequently difficult to diagnose clinically in its early stages because of confounding signs and symptoms of congestive orbitopathy. We evaluated the ability of square area measurements of orbital apex crowding, calculated with MDCT, to detect DON.

MATERIALS AND METHODS: Fifty-six patients with GO were studied prospectively with complete neuro-ophthalmologic examination and MDCT scanning. Square measurements were taken from coronal sections 12 mm, 18 mm, and 24 mm from the interzygomatic line. The ratio between the extraocular muscle area and the orbital bone area was used as a CI. Intracranial fat prolapse through the superior orbital fissure was recorded as present or absent. Severity of optic nerve crowding was also subjectively graded on coronal images. Orbits were divided into 2 groups (with or without clinical evidence of DON) and compared.

RESULTS: Ninety-five orbits (36 with and 59 without DON) were studied. The CIs at all 3 levels and the subjective crowding score were significantly greater in orbits with DON ($P < .001$). No significant difference was observed regarding intracranial fat prolapse ($P = .105$). The area under the ROC curves was 0.91, 0.93, and 0.87 for CIs at 12, 18, and 24 mm, respectively. The best performance was at 18 mm, where a cutoff value of 57.5% corresponded to 91.7% sensitivity, 89.8% specificity, and an odds ratio of 97.2 for detecting DON. A significant correlation ($P < .001$) between the CIs and VF defects was observed.

CONCLUSIONS: Orbital CIs based on area measurements were found to predict DON more reliably than subjective grading of orbital crowding or intracranial fat prolapse.

ABBREVIATIONS: CI = crowding index; DON = dysthyroid optic neuropathy; GO = Graves orbitopathy; HU = Hounsfield unit; MDCT = multidetector CT; ROC = receiver operating characteristic; SAP = standard automated perimetry; VA = visual acuity; VF = visual field; WL = window level; WW = window width

GO is an autoimmune inflammatory process affecting the orbital and periorbital tissues, mainly the extraocular muscles but also the retrobulbar fat. GO may occur before, during, or after the onset of hyperthyroidism or, less frequently, in euthyroid or hypothyroid patients.¹ The enlargement of the extraocular muscles is responsible for most of the debilitating manifestations of the disease, including proptosis, diplopia, congestive signs, and DON.²⁻⁵

DON is a serious complication of GO occurring in 3.4% of patients,⁶ almost always as a result of optic nerve compression at the orbital apex by enlarged extraocular muscles. The diagnosis of DON rests mainly on clinical findings such as decreased VA, abnormal VFs, altered color and brightness perception, delayed visual evoked potentials, afferent pupillary defects, and edema or atrophy of the optic nerve head.⁷ In many cases, however, DON is subclinical and difficult to diagnose due to confounding signs and symptoms, notably significant orbital congestion or decreased corneal transparency from exposure keratopathy.⁸ Establishing a diagnosis of DON

may also be difficult because many tests of optic nerve dysfunction, such as VA, color and brightness perception, and VF, especially when performed with standard automated perimetry, require the full cooperation of an alert and motivated patient and will not infrequently render false-positive results, particularly in patients with congestive GO. Because the prognosis of DON improves significantly with early diagnosis and treatment, much effort has been placed on designing objective tests capable of identifying patients at high risk for developing DON.⁹

CT is the preferred imaging technique for investigating DON.¹ Several studies have tested the ability of CT parameters (linear,^{3,9-11} area, and volume¹²⁻¹⁴ measurements of the orbital muscles) to facilitate the diagnosis of DON. Most of these studies used axial and direct or reformatted coronal images acquired with conventional CT scanners, and calculations were often performed manually from hard copies of the scans. Subjective assessment of apical crowding based on coronal images described by Nugent et al,¹⁵ and detection of intracranial fat prolapse introduced by Birchall et al,¹⁶ have also been used to evaluate the risk of development of DON.

The purpose of this study was to objectively quantify orbital apical crowding by calculating the ratio between extraocular muscle area and orbital bone area at 3 distinct coronal planes using MDCT, and to test the ability of such ratios to detect DON. In addition, we tested for possible correlations

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HEAD & NECK

ORIGINAL RESEARCH

Fig 1. Flow chart demonstrating inclusions and exclusions of patients and orbits, with or without DON, in the study.

between clinical parameters of orbits with DON and CT square area measurements, and we compared the muscle area/bone area ratios calculated with MDCT to assessment of orbital fat prolapse¹⁶ and apical crowding, based on subjective assessment of coronal images.¹⁵

Materials and Methods

This study followed the principles of the Declaration of Helsinki and was approved by our institutional review board. Sixty-nine patients with GO (47 women, 22 men) were studied prospectively between July 2005 and September 2010. GO was diagnosed in accordance with previously defined criteria.¹⁷ All patients had bilateral GO and symptoms related to the orbitopathy were present for a period of time ranging from 2 weeks to 2 years. Patients underwent a complete neuro-ophthalmologic examination by an experienced neuro-ophthalmologist (M.L.R.M.), including best-corrected VA, applanation tonometry, pupillary reactions, extraocular motility evaluation, slit lamp examination, evaluation of soft tissue and eyelid inflammation, measurement of lid fissure, Hertel exophthalmometry, fundoscopy, and VF evaluation.

VF was performed using manual perimetry and standard automated perimetry. Manual VF testing was performed using the Goldmann perimeter (Haag-Streit, Bern, Switzerland). The V-4-e, I-4-e, I-3-e, I-2-e, and I-1-e stimuli were used to draw the isopters. Kinetic determinations were followed by static presentation of the stimuli, particularly in the central 30-degree area, to search for localized defects. Standard automated perimetry was performed with a Humphrey field analyzer 750 (Zeiss-Humphrey, Dublin, California) using the 24-2 SITA-Standard strategy. The patients' appropriate near correction was used. Rest breaks were allowed when requested. To qualify as an abnormal VF on standard automated perimetry, 3 adjacent abnormal points at $P < .05$, or 2 adjacent points with 1 abnormal point at $P < .01$, were required.¹¹ Exclusion criteria were age younger than 20 years, poor cooperation for performing VF examination, spherical refraction over ± 5 diopters, cylinder correction over ± 3 diopters, and an unreliable VF. An unreliable Humphrey VF test was

defined as one with greater than 25% fixation losses, false-positive, or false-negative responses. Patients with clinical signs of glaucomatous optic neuropathy, cataract, cornea transparency abnormalities, retinal diseases, previous orbital or strabismus surgery, and other types of neuropathies were also excluded.

Orbits of eyes with GO and visual function data clearly indicating the presence or absence of DON, based on the neuro-ophthalmologic examination, were eligible. The diagnostic criteria for DON were 1) presence of a relative afferent papillary defect, and 2) presence of a well-defined VF defect. Patients with nonreproducible VF abnormalities and ocular or optic nerve diseases preventing correct diagnosis of DON were excluded. All patients with DON had GO in the congestive phase of the disease, with onset of visual disturbance and clinical signs of orbital congestive disease within less than 4 weeks.

Thirteen of the 69 patients did not qualify based on inclusion and exclusion criteria. The remaining 56 patients (36 women) had 95 orbits included in the study, grouped into orbits with and without DON. The first group included 36 orbits of 23 patients with DON. In this group, 10 orbits were not included in the analysis either because DON was unilateral ($n = 7$), the presence or absence of DON could not be established with certainty on 1 side ($n = 2$), or a previous central retinal artery occlusion precluded correct diagnosis of DON ($n = 1$). The second group included 59 orbits from 33 patients in which DON was clearly absent. Seven orbits were excluded from this group because of difficulties in establishing the presence or absence of DON; in 6 cases, VF abnormalities were questionable, even after repeat examination, and in 1 case, severe eye deviation due to extraocular involvement precluded proper VF examination (Fig 1). The data from the 2 groups of orbits were compared.

Within a period of 2 weeks after the clinical examination, all patients were scanned on a 16-section MDCT scanner (MX 8000 IDT16; Philips Medical Systems, Best, the Netherlands) without the use of sedation or intravenous contrast. Patients were scanned with their eyes closed and steady in primary position of gaze. The scanning parameters were 120 Kv, 150 mAs, detector configuration 16×0.75 mm, 1.5-mm section thickness, and 0.7-mm section increment. Im-

Fig 2. Schematic representation of the CT study. *Left*, Axial scan with planning details of contiguous coronal sections. *Right*, Coronal images taken 12, 18, and 24 mm from the interzygomatic line.

Fig 3. *Left*, Example of reformatted coronal section 18 mm from the interzygomatic line. A region of interest was drawn freehand around the bony orbital rim for automatic calculation of the total area of orbital content (*bottom right*). Area measurements of muscles and soft tissues were obtained based on a predefined range in HU (*top right*). The CI was calculated from the ratio between the soft tissues and the total orbital area. The range of thresholds in HU excluded bone tissue from analysis in all measurements.

ages were postprocessed at a dedicated workstation (Extended Brilliance Workspace V3; Philips Medical Systems) and were analyzed by a head and neck radiologist (L.N.S.) blinded to the clinical condition of the patients.

One-mm coronal slabs were reformatted from contiguous axial sections of the orbit and realigned if any asymmetry was observed. The slabs were reformatted from the orbital rim up to the orbital apex (Fig 2) and evaluated at planes located 12 mm, 18 mm, and 24 mm from that interzygomatic line, defined as the line between the anterior margins of the frontal processes of zygomatic bones at the level of optic nerve plane (Fig 2). Muscular crowding was calculated at each of these planes using a thresholding-based technique (available at the workstation) to calculate the area of extraocular muscle and orbital bone. The software is able to calculate the volumetric measurements of the structures within the slabs. Because we were interested in measuring the area of extraocular muscle and orbital bone, we generated volumes from a 1-mm thick slab, which would correspond numerically to their areas.

A predefined range of threshold was determined to separate soft tissue, which mainly includes muscles, nerves, and vessels from other orbital tissues, which mainly include fat. The thresholds were then set at 40/100 HU (WL/WW) for soft tissue and at $-160/230$ HU (WL/WW) for the whole orbital content (Fig 3). For each of the preset coronal planes, a region of interest was drawn freehand around the orbital bone rim, so the software could automatically calculate the ratio between the total area of orbital content and the area of soft

tissue in the region of interest, thus obtaining the ratio between these as the orbital CI (Fig 3). Bone tissue within the region of interest was not included in any measurement because it is outside the predefined range of thresholds.

The same reader (a practicing radiologist for over 6 years) repeated the measurements for 22 randomly selected orbits (10 with DON) approximately 6 months after the first measurements. On a different occasion, the same group of orbits was independently measured by a senior radiologist (E.M.M.S.G.) with approximately 20 years of practice. Both readers were blinded to the presence or absence of DON.

A categoric score of orbital apical crowding, as described by Nugent et al,¹⁵ was also determined at a predetermined coronal section at the midpoint of the intraorbital optic nerve. The score reflects circumferential effacement of perineural fat by the extraocular muscles (0 = none; 1 = mild, 1%–25%; 2 = moderate, 25%–50%; 3 = severe, >50%).¹⁵ Finally, we assessed each set of images for the presence of intracranial fat prolapse through the superior orbital fissures (recorded as present or absent) using the method described by Birchall et al.¹⁶

Statistical Analysis

Descriptive statistics included mean values ($\pm$ SD) for normally distributed variables. Analysis of histograms and the Shapiro-Wilk test were used to evaluate the normality assumption. We used a χ^2 or Fisher exact test for comparison of qualitative variables and an un-

Table 1: Mean $\pm$ SD of orbital CI calculated at 12 mm, 18 mm, and 24 mm from the interzygomatic line, and presence or absence of intracranial fat prolapse and categoric scores of orbital crowding (Nugent score) in orbits of patients with GO with or without DON

Parameter	Orbits with DON (n = 36)	Orbits without DON (n = 59)	P value
Mean $\pm$ SD 12 mm (95% conf. int)	0.51 $\pm$ 0.13 (0.21–0.80)	0.29 $\pm$ 0.09 (0.11–0.51)	<0.001*
Mean $\pm$ SD 18 mm (95% conf. int)	0.71 $\pm$ 0.12 (0.33–0.89)	0.42 $\pm$ 0.13 (0.20–0.72)	<0.001*
Mean $\pm$ SD 24 mm (95% conf. int)	0.77 $\pm$ 0.11 (0.42–1.00)	0.57 $\pm$ 0.15 (0.26–0.84)	<0.001*
Intracranial fat prolapse	12 (33.3%)	11 (18.6%)	0.105**
Nugent crowding score ≥ 1	29 (80.6%)	9 (15%)	<0.001***

Note:—Conf. int. indicates confidence interval.

* Student *t* test.

** χ^2 test.

*** Fisher exact test.

Fig 4. A, Axial CT of a patient with bilateral DON and lack of fat prolapse through the superior ophthalmic fissure. The positions of the superior ophthalmic fissures are shown by thin dashed lines. B, Axial CT of a patient without DON and showing bilateral fat prolapse through the ophthalmic fissure. The positions of the superior ophthalmic fissures are shown by thin dashed lines.

paired *t* test for comparisons of continuous normally distributed parameters corresponding to the mean CIs at planes located 12, 18, and 24 mm from the interzygomatic line. ROC curves were used to describe the ability of CI to discriminate orbits with from those without DON. For each parameter, sensitivities at fixed specificities of 80% and 95% were calculated. ICC was calculated to assess inter- and intrarater variability for measurements of CIs at 12, 18, and 24 mm from the interzygomatic lines. The sensitivity and specificity of the Nugent score and the presence of intracranial prolapse were also calculated. Accuracy and odds ratio for having DON were calculated. Spearman ranked correlation coefficients (*p*) were used to assess the relationship between VF sensitivity loss and the CT parameters analyzed. A *P* value <.05 was considered statistically significant. The statistical analyses were performed using the software SPSS v.15.0 (SPSS, Chicago, Illinois).

Results

Ninety-five orbits of 56 patients with GO met the inclusion criteria and were included in the analysis. Thirty-six of these were from 23 patients (12 women and 11 men; mean age $\pm$ SD, 53.6 $\pm$ 10.6 years) who met the diagnostic criteria for DON. Fifty-nine orbits were from 33 patients (24 women and 9 men; mean age $\pm$ SD, 42.0 $\pm$ 10.0 years) affected by GO but not with DON (Fig 1).

The VA of the 36 eyes with DON was 1.0 (*n* = 19), 0.9 (*n* = 6), 0.8 (*n* = 5), 0.6 (*n* = 2), 0.5 (*n* = 2), 0.2 (*n* = 1), and 0.1 (*n* = 1). The mean ($\pm$ SD) SAP mean deviation in eyes with DON was -10.37 ± 7.38 dB. The glaucoma hemifield test yielded results outside the normal range in 29 eyes and borderline in 5. Exophthalmometry measurements in affected eyes ranged from 19–32 mm (mean $\pm$ SD, 25.03 $\pm$ 3.11 mm). Restrictive myopathy was present in all orbits with DON. The fundoscopic examination revealed optic disc edema in 6 eyes, optic disc pallor in 1, and no abnormalities in the remainder.

In the group without DON, VA was 1.0 in all eyes and exophthalmometry findings ranged from 16.0 to 31.5 mm (mean $\pm$ SD, 23.5 $\pm$ 2.7).

Table 1 shows mean values ($\pm$ SD) and range for orbital apex CI values at different positions in the coronal plane, as well as the percentage of orbits with intracranial fat prolapse, in both groups of patients. Table 1 also presents and compares categoric scores of orbital apex crowding (Nugent score) greater than 0 for both groups. In all coronal planes measured, the mean CI values were significantly greater in orbits with DON than in orbits without DON (*P* < .001). There were statistically significant differences between the 2 groups of orbits with regard to the presence of orbital apex crowding, as defined by the Nugent score, but no difference was observed regarding the presence of intracranial fat prolapse (Fig 4).

The ICC for the CI measurements by the second observer at 12, 18, and 24 mm was 0.88, 0.97, and 0.96, respectively (*P* < .001), indicating an excellent interobserver variability. Corresponding values for repeated measurements by the same reader were 0.88, 0.99, and 0.98, indicating excellent intraobserver variability (*P* < .001).

Figure 5 shows ROC curves for the 3 CIs. The area under the ROC curve was 0.91, 0.93, and 0.87 at 12, 18, and 24 mm, respectively, from the interzygomatic plane. In other words, the CI at 18 mm (0.93) was the most efficient indicator of DON. Cutoff values were determined for the 3 indexes to calculate the sensitivity and specificity of the CIs, differentiating the 2 groups of orbits. Sensitivity, specificity, accuracy, and positive and negative predictive values of the categoric scores (Nugent score and intracranial fat prolapse) for the main cutoffs of the 3 CIs are presented in Table 2. The best sensitivity/specificity ratio was found for the CI value of 0.575 at 18 mm from the interzygomatic plane (sensitivity 91.7%, specificity 90.0%, accuracy 90.5, odds ratio for detecting DON 97.2).

Fig 5. ROC curves of the 3 CI parameters for the discrimination between orbits with and without DON.

Table 3 shows the associations between CT parameters and VF loss based on mean deviation on computerized perimetry. A significant correlation was observed for all parameters studied, but the highest correlation was observed for the parameter CI at 18 mm ($\rho = 0.62$, $R^2 = 38\%$, $P < .001$), with greater CT parameter values associated with greater VF defect (lower mean deviation values). Figure 6 shows a scatterplot of CI measurements at 18 mm from the interzygomatic plane versus VF mean deviation values.

Discussion

A significant complication of GO, DON requires prompt diagnosis and treatment to prevent permanent damage to visual function. Although inflammatory and vascular mechanisms have been suggested, direct compression of the optic nerve by enlarged extraocular muscles at the orbital apex is the most widely accepted theory to explain the development of DON. The theory is based mostly on CT imaging studies confirming the presence of orbital apex crowding in most patients with DON.^{10,12,13,18,19}

Because of its great importance in DON, apical crowding is quantified with a score first described by Nugent et al¹⁵ and reproduced by many other authors,^{1,3,7,9,16} which grades the effacement of the perineural fat as 0 (none), 1 (up to 25%), 2 (25%–50%), or 3 (greater than 50%).¹⁵ Using this method, Nugent et al found severe apical orbital crowding (grade 3) in 12 of 18 orbits with DON but in only 16 of 124 orbits without DON.¹⁵ Neigel et al graded as moderate or severe crowding 79.2% of orbits with DON but only 12.9% of orbits without DON.⁷ Birchall et al found severe apical crowding to be a good predictor of DON, with a sensitivity of 62% and a specificity of 91%.¹⁶ A recent multicenter study found apical muscle crowding in 49 of 56 orbits with DON.¹ In another study, severe optic nerve crowding was retrospectively noted in 80% of orbits (16 of 20) with optic neuropathy compared with 29% of orbits without DON (10 of 34). No orbits with optic neuropathy scored lower than grade 2.³ Chan et al⁹ studied 32 orbits

with DON, of which only 2 were given an apical crowding score ≤ 1 .

In our study, although the subjective orbital apex CI detected DON with 80.6% sensitivity for scores 1 or 2, none of the 36 affected orbits presented grade 3 apical crowding. These findings are remarkably different from previous studies using the Nugent subjective score to detect DON,^{1,3,9,15} probably due to differences in subjective criteria for defining and grading apical crowding. While it seems clear that the Nugent apical crowding score is useful to raise suspicion of the presence of DON, it does not provide a clear definition of the position along the orbit where the coronal plane is used to determine it, nor does it provide a clear differentiation between grades 1, 2, and 3.

We attempted to move 1 step further by objectively quantifying apical crowding at a well-defined coronal plane using MDCT. The technique was made possible by the introduction of MDCT scanners, which make quantitative measures readily available and allow the orbital structures to be reformatted with precision. Our patients were prospectively evaluated for the presence or absence of DON, and a large number of orbits with optic neuropathy were included. Finally, the different CT parameters were submitted to a prospective comparison. Our results show that patients with DON are more efficiently discriminated with the orbital apex crowding score than with the Nugent subjective score, with greater sensitivity/specificity for each index especially at 18 mm from the interzygomatic line. Measurements were found to be reproducible with very high inter- and intraobserver ICC. At all 3 CIs, the 2 groups (with and without DON) differed significantly. The best result was obtained at 18 mm (ROC curve area 0.93). At the 57.5% cut-off, CI at 18 mm reached a sensitivity of 91.7%, a specificity of 89.9% and an odds ratio of 97.2 for detecting DON. This was significantly better than the discrimination ability of both the Nugent score and intracranial fat prolapse (Table 2). It also represents a significant improvement over the performance of the Nugent score in 4 previous studies.^{1,3,15,16} Another finding from our study was that, at each point, CI was strongly correlated with VF loss assessed by VF mean deviation (Table 3).

Using MDCT, we revisited the method described by Birchall et al.¹⁶ Unlike the original report, in our study, orbits with or without DON did not differ statistically with regard to intracranial fat prolapse through the superior orbital fissure. MDCT made it possible to view orbital fat prolapse at exactly the same reference points described by the authors, but the results were not predictive of DON in either group. Other researchers have reached similar conclusions.^{1,9}

Finally, our study shows that CI is more efficient at detecting DON than the linear muscle index described by Barrett et al.¹⁰ In their study, a muscle index of 67% or greater indicated compressive neuropathy and had a diagnostic sensitivity of 67%.¹⁰ In a previous study using MDCT to determine the sensitivity and specificity of the muscle index in a similar set of patients, we found that a muscle index of 60% provided the best combination of sensitivity/specificity (79% and 72%, respectively).¹¹

Other CT features have been studied as indicators of DON, such as lacrimal gland displacement, exophthalmos, superior ophthalmic vein dilation, and single muscle measurements, with poor or inconclusive results.^{3,7,10,15,16,19} Chan et al⁹ high-

Table 2: Sensitivity, specificity, accuracy, and odds ratio for different cutoff values of CI as well as for Nugent score and the presence of intracranial fat prolapse

Parameter	Cutoff Value	Sensitivity/Specificity	Accuracy (95% conf. int.)	Odds Ratio (95% conf. int.)
Crowding index at 12 mm	38.5%	80.6%/81.4%	80.0 (69.9–87.5)	15.3 (4.9–49.3)
Crowding index at 18 mm	57.5%	91.7%/89.8%	90.5 (80.2–95)	97.2 (19.6–572.9)
Crowding index at 24 mm	72.0%	83.3%/81.4%	82.1 (72.3–88.8)	21.8 (6.5–77.2)
Fat prolapse	presence	33.3%/81.4%	0.63 (53.9–72.0)	2.2 (0.8–6.3)
Subjective crowding score	≥1	58.3%/84.7%	74.7 (64.6–82.8)	7.8 (2.7–23.3)

Note:—Conf. int. indicates confidence interval

Table 3: Associations between CT parameters and VF loss expressed in decibels

CT Parameter	VF Loss (dB)	
	ρ^*	P
Crowding index at 12 mm	0.56	<0.001**
Crowding index at 18 mm	0.62	<0.001**
Crowding index at 24 mm	0.54	<0.001**
Intracranial fat prolapse	0.22	0.033**
Subjective crowding score	0.33	0.001**

*Spearman rank correlation coefficient; ** significant values.

Fig 6. Scatterplots depicting the relationship between CI values measured at 18 mm from the interzygomatic rim and VF mean deviation expressed in decibels in patients with (closed circles) or without (open circles) DON.

lighted the importance of using both extraocular muscle enlargement and bony orbit anatomy to predict DON, with narrow bony orbits found to be an independent predictor of DON. With our method, because orbital apex CIs express a ratio between the area of soft tissue and the total orbital area, they combine the ability of both parameters to predict DON.

Conclusions

Our study evaluated the ability of the quantitative area index of apical crowding, which is easily calculated on clinical

workstations, to predict DON and found it to be an improvement over previously described methods. Further prospective studies will be helpful to validate our findings.

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5.4 Artigo de medidas volumétricas

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CLINICAL SCIENCE

Predicting dysthyroid optic neuropathy using computed tomography volumetric analyses of orbital structures

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OBJECTIVE: To evaluate the ability of orbital apex crowding volume measurements calculated with multidetector-computed tomography to detect dysthyroid optic neuropathy.

METHODS: Ninety-three patients with Graves' orbitopathy were studied prospectively. All of the patients underwent a complete neuro-ophthalmic examination and computed tomography scanning. Volumetric measurements were calculated from axial and coronal contiguous sections using a dedicated workstation. Orbital fat and muscle volume were estimated on the basis of their attenuation values (in Hounsfield units) using measurements from the anterior orbital rim to the optic foramen. Two indexes of orbital muscle crowding were calculated: i) the volumetric crowding index, which is the ratio between soft tissue (mainly extraocular muscles) and orbital fat volume and is based on axial scans of the entire orbit; and ii) the volumetric orbital apex crowding index, which is the ratio between the extraocular muscles and orbital fat volume and is based on coronal scans of the orbital apex. Two groups of orbits (with and without dysthyroid optic neuropathy) were compared.

RESULTS: One hundred and two orbits of 61 patients with Graves' orbitopathy met the inclusion criteria and were analyzed. Forty-one orbits were diagnosed with Graves' orbitopathy, and 61 orbits did not have optic neuropathy. The two groups of orbits differed significantly with regard to both of the volumetric indexes ($p < 0.001$). Although both indexes had good discrimination ability, the volumetric orbital apex crowding index yielded the best results with 92% sensitivity, 86% specificity, 81%/94% positive/negative predictive value and 88% accuracy at a cutoff of 4.14.

CONCLUSION: This study found that the orbital volumetric crowding index was a more effective predictor of dysthyroid optic neuropathy than previously described computed tomography indexes were.

KEYWORDS: Dysthyroid optic neuropathy; Multidetector computed tomography; Graves' orbitopathy; Volume CT.

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INTRODUCTION

Graves' orbitopathy (GO) is the most common extrathyroid manifestation of Graves' disease (GD). It occurs before, during, or after the onset of hyperthyroidism and, less frequently, in euthyroid or hypothyroid patients. The course of GO can be divided into active (congestive) and inactive (fibrotic) phases. Tissue expansion occurs within the relatively fixed volume imposed by the bony orbit and results in inflammation, the accumulation of hydrophilic

glycosaminoglycans and increased fat content (1). Clinical signs include proptosis, congestive signs, strabismus, and dysthyroid optic neuropathy (DON) (2-5).

DON is the most significant complication of GO. It affects 3.4 to 8% of GO patients (6-9) and requires prompt treatment to avoid permanent visual loss. Almost all instances of DON result from optic nerve compression at the orbital apex by enlarged extraocular muscles. The diagnosis of DON includes the following clinical features: decreased visual acuity (VA), abnormal visual fields (VF), impaired color and brightness perception, delayed visual evoked potentials, afferent pupillary defects and edema or atrophy of the optic nerve head (6). Unfortunately, some of these tests require the full cooperation of an alert and motivated patient and often render false positive results, particularly in patients with congestive GO. Furthermore, alternative causes of visual impairment secondary to GO,

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such as exposure keratopathy or secondary glaucoma, and coincidental conditions, such as amblyopia or cataracts, may also contribute to the considerable difficulty of detecting DON (10). Because diagnosing DON can be clinically difficult and because its prognosis improves significantly with early diagnosis and treatment, it is important to design objective tests that can identify patients at risk for developing DON (11).

Computed tomography (CT) is the most frequently used imaging modality in patients with GO because of its capacity to visualize bone and soft tissue in the orbit. Previous studies have shown that a number of CT scan parameters can help to detect and facilitate the diagnosis of DON, primarily those parameters based on the detection of orbital apical crowding by enlarged extraocular muscles (4-6,12-16). Crowding has been successfully estimated with CT parameters, such as linear measurements of extraocular muscles (4,5,11,13), the subjective assessment of apical crowding (on single coronal images) (4,11,16,17) and measurements of the area (11) and volume (18,19) of the orbital muscles.

Although linear and area measurements have proven to be helpful in the diagnosis of DON, the assessment of orbital apex crowding using volumetric estimates of structures could potentially improve the ability to detect and diagnose DON. In fact, Feldon et al. (2,18) used volumetric estimates of orbital contents to investigate the risk of developing DON in GO patients; however, those authors' measurements required cumbersome manual calculations of the orbital muscles and other orbital structures. The recent introduction of multidetector-row computed tomography (MDCT) has resulted in shorter scanning times and higher resolution and has made it possible to reformat images from any plane, making orbital measurements easier to take and more precise. Using software for three-dimension orbital structure analysis, volumetric measurements can be easily calculated at a workstation (20).

The purpose of this study was therefore to quantify muscle crowding and use it to test the ability of two volumetric indexes of muscle crowding based on volume measurements obtained with multidetector-computed tomography to predict DON in the orbits of GO patients.

PATIENTS AND METHODS

The study followed the tenets of the Declaration of Helsinki and was approved by an institutional ethics committee. Ninety-three new patients with GO who were admitted to the orbit service of a tertiary referral eye center during the five-year study period were prospectively included. GO was diagnosed in accordance with previously established criteria (21). All of the patients underwent a complete neuro-ophthalmic examination, including best-corrected VA, applanation tonometry, pupillary reactions, extraocular motility evaluation, slit lamp examination, soft tissue and eyelid inflammation evaluation, lid fissure measurement, Hertel exophthalmometry, funduscopy, and VF evaluation.

VF testing was performed using manual perimetry and standard automated perimetry (SAP). Manual VF testing was performed using the Goldmann perimeter (GP) (Haag-Streit AG, Bern, Switzerland). SAP was performed with a Humphrey Field Analyzer 750 (Zeiss-Humphrey, Dublin, CA) using the 24-2 SITA-Standard strategy. The patients'

appropriate near correction was used. To qualify as an abnormal VF on SAP, three adjacent abnormal points at the $p < 0.05$ level or two adjacent points with one abnormal point at the $p < 0.01$ level on the pattern deviation plot were required (22). Exclusion criteria included the following: age under 20 years, inability to cooperate with VF testing, spherical refraction over +5 D, cylinder correction over +3 D and unreliable VF test results. An unreliable Humphrey VF test was defined as one with more than 25% fixation losses, false-positive or false-negative responses. Patients with clinical signs of glaucomatous optic neuropathy, optic disc anomaly, optic media opacities, previous orbital or strabismus surgery, and other types of neuropathies were also excluded.

All patients were scanned with a 16-slice MDCT scanner (Brilliance 16; Philips Medical Systems, Nederland B.V., The Netherlands) without the use of sedation or intravenous contrast. The CT scans were obtained using contiguous axial slices, with the patient's head positioned parallel to the Frankfurt plane. The patients were instructed to keep their eyes closed and steady in the primary gaze position. The scanning parameters were as follows: 120 Kv, 200 mAs, 16x0.75 mm detector configuration, 1.5 mm slice thickness and 0.7 mm slice increment. The images were postprocessed at a dedicated workstation and read by a single head-and-neck radiologist (L.N.S.) who was blinded to the patients' clinical condition.

Two volumetric indexes were calculated, one based on axial scans of the entire orbit content (up to the orbital rim) and one based on coronal scans of the orbital content from the midpoint of the orbital segment of the optic nerve to the orbital entrance of the optic canal.

Volume measurements of the entire orbit from axial scans

To calculate volumes for the whole orbital content, contiguous axial scans were analyzed. The different tissues were color-coded according to their attenuation in Hounsfield units (HU). Tissue HU thresholds were defined using different window levels (WL) and window widths (WW) to separate the soft tissue (which mainly includes muscles, nerves and vessels) from other orbital tissues (mainly fatty content). Orbital soft tissue thresholds were set at 40/100 HU (WL/WW), and the fat tissue threshold was set at -160/230 HU (WL/WW). For the tissue volume measurements, each axial slice was traced along the bony orbit limits. The anterior boundary of the orbit was delineated by a straight line connecting the lateral and the medial orbital rim (Figure 1). The marking began at the topmost axial slice containing the orbit and continued downwards, slice by slice, until all of the orbit content was included. The volume of the muscles (including vessels and nerves), soft tissues and fat within the marked space was then estimated with the software (Figure 1). The volumetric orbital muscle crowding index (VCI) was calculated as the ratio between the soft tissue volume and the fat tissue volume.

Volume measurements of the orbital apex from coronal scans

One-millimeter coronal CT slabs were reformatted from contiguous axial slices of the orbit, which includes the space between the interzygomatic line and the orbital apex (Figure 2). The orbital volume was calculated from the

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Figure 1 - A, B and C. Examples of the area outlined on 3 axial slices of computed tomography scans, from which measurements were obtained. Representation of the soft tissue (mostly muscles; D) and orbital fat (E) volumes based on measurements of the sequential axial slices.

posterior portion of the orbit, which encompasses the tissues within a point in the optic nerve halfway between the globe and the orbital apex and up to the entrance of the optic canal. The fat and soft tissues were color-coded with the same settings used for the axial measurements. For each of the preset coronal planes, a region of interest was traced around the orbital bone rim (Figure 2). The software automatically calculated the total volume of fat and soft tissue in that region (Figure 2). The ratio of the soft tissue volume to the fat volume (using volume measures taken at the apex) was calculated to determine the volumetric orbital apex crowding index (VACI).

The same reader repeated the measurements for 26 randomly selected orbits (13 with DON) approximately

eight months after the first measurements. On a different occasion, the same group of orbits was independently measured by a senior radiologist (E.M.M.S.G.). Both readers were blinded to the presence or absence of DON.

GO patients' eyes for which visual function data clearly indicated the presence or absence of active DON were considered eligible for the study. The criteria used to diagnose DON included the following: 1) The presence of a confirmed VF defect on SAP or GP associated or not with diminished best-corrected VA and not caused by changes in transparency and 2) in unilateral and asymmetric cases, the presence of a relative pupillary defect. When the best-corrected VA was normal and VF abnormalities were present on SAP, a repeat examination using SAP or GP was performed to rule out false-positive responses. Therefore, only eyes with confirmed VF defects were included in the analysis. Eyes with normal VA and nonreproducible VF abnormalities on repeat examinations were excluded. Patients with ocular or optic nerve diseases that could interfere with the diagnosis of DON were also excluded. All patients with DON had active disease, visual disturbance within three months of the onset of the disease and clinical signs of orbital congestive disease. Patients from the group without DON had a history of orbital disease ranging from two months to four years. The findings for the two groups were compared.

Statistical analysis

Descriptive statistics included the mean values $\pm$ SD for normally distributed variables. Receiver operating characteristic (ROC) curves were used to describe the ability of the VCI and the VACI to discriminate between orbits with and without DON. For each parameter, sensitivities at the fixed specificities of 80% and 95% were calculated. Sensitivity, specificity, likelihood ratio, and accuracy were calculated for the best cutoff values of VCI and VACI. The intraclass

Figure 2 - Percentage difference from rest to ventilatory anaerobic threshold (rest/VAT), rest to respiratory compensation point (rest/RCP) and rest to peak of exercise (rest/Peak) in patients with coronary artery disease subjected to continuous exercise training (panel A) and interval exercise training (panel B). VAT=ventilatory anaerobic threshold; RCP=respiratory compensation point. * $p < 0.05$ vs. post-intervention.

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correlation coefficient (ICC) was calculated to assess the interrater and intrarater variability for the VCI and VACI measurements. A *p*-value less than 0.05 was considered statistically significant.

RESULTS

Thirty-two of the 93 patients were excluded based on the above-described criteria. The remaining 61 patients (37 women and 24 men) had 102 orbits that were included in the study. The orbits were divided into two groups according to the presence or absence of DON. The first group included 41 orbits of 27 patients (12 women and 15 men; mean age $\pm$ SD: 53.8 ± 10.1 years) who met the diagnostic criteria for DON. Fourteen patients had bilateral DON; for those patients, both orbits were included in the study. Thirteen patients had only one orbit included in the DON group. Of these 13 patients, the contralateral eye of ten patients did not meet the DON criteria. Two patients had the contralateral eye excluded because the presence or absence of DON could not be clearly determined; in one patient, a history of central retinal artery occlusion unrelated to GO excluded the contralateral eye. The second group included 61 orbits in which DON was clearly absent from 34 patients (25 women and nine men; mean age $\pm$ SD: 42.3 ± 10.2 years). In this group, seven orbits were excluded from analysis because of the uncertainty of the DON diagnosis. Six of these patients had questionable VF abnormalities on SAP even after repeat examinations. One patient had an eye with severe deviations caused by extraocular muscle involvement, which precluded proper VF examination.

For the 41 orbits with DON, the best-corrected VA was 1.0 in 20 patients, 0.9 in seven patients, 0.8 in six patients, 0.7 in one patient, 0.6 in two patients, 0.4 in one patient, 0.5 in two patients, 0.2 in one patient, and 0.1 in one patient. Exophthalmometry measurements in the affected eyes ranged from 19 to 32 mm (mean $\pm$ SD: 25.14 ± 3.19 mm). Restrictive myopathy was present in all orbits with DON. The fundoscopic examination revealed optic disc edema in eight eyes, optic disc pallor in one and no abnormalities in the remainder. In the group without DON, the best-corrected VA was 1.0 in all eyes, and exophthalmometry findings ranged from 16.0 to 31.5 mm (mean $\pm$ SD: 23.4 ± 2.7).

Table 1 shows the mean $\pm$ SD and the ranges for the VCI and VACI. The mean VCI and VACI values were significantly higher in the orbits with DON ($p < 0.001$).

Table 2 compares the two groups' areas under ROC curves for the two volumetric indexes, with confidence intervals and sensitivity at the 95% and 80% specificity rates. The area under the ROC curve was 0.86 for the VCI and 0.92

Table 1 - Means $\pm$ standard deviation of the axial volumetric orbital crowding index (VCI) and the coronal volumetric orbital apex crowding index (VACI) in the orbits of patients with Graves' orbitopathy (GO) with or without dysthyroid optic neuropathy (DON).

Parameter	Orbits with DON n=41	Orbits without DON n=61	<i>p</i> -value*
Mean $\pm$ SD VCI	1.84 $\pm$ 1.02	0.83 $\pm$ 0.28	<i><0.001</i>
95% CI	1.52–2.16	0.76–0.90	
Range	0.31–5.28	0.34–1.53	
Mean $\pm$ SD VACI	21.35 $\pm$ 21.09	2.82 $\pm$ 2.28	<i><0.001</i>
95% CI	14.69–28.01	2.24–3.40	
Range	1.03–86.52	0.59–10.97	

*Student's *t*-test. Significant values are in italics. CI=confidence interval.

for the VACI. Cutoff values were determined for the two indexes to calculate their sensitivity and specificity for differentiating orbits with and without DON. The best sensitivity/specificity ratio was achieved with a VACI cutoff of 4.14 (sensitivity: 90%, specificity: 87%, likelihood ratio: 6.9, accuracy for detecting DON: 88%; Table 2).

The ICCs for the VCI and VACI as determined by the second observer were 0.90 and 0.91, respectively ($p < 0.001$), indicating an excellent interobserver variability. Corresponding values for repeated measurements by the same observer were 0.90 and 0.89, indicating excellent intraobserver variability ($p < 0.001$).

DISCUSSION

GO can be an insidious disease, and DON is a significant complication that requires prompt diagnosis and treatment to prevent permanent visual damage. Although research has suggested that DON may be caused by inflammatory and vascular mechanisms, the most widely accepted theory for DON development is direct compression of the optic nerve by enlarged extra ocular muscles at the orbital apex (3,6,23,24). The diagnosis of DON depends mainly on clinical features based on visual function assessment, afferent pupillary defect and fundoscopic abnormalities. Nevertheless, DON is often subclinical and in many cases, it is difficult to diagnose because of confounding signs and symptoms. Furthermore, patients with severe orbitopathy tend to have more congestive and oculomotor symptoms, which may outweigh or mask subtle visual deterioration (6). Therefore, the development of imaging techniques that facilitate the diagnosis of DON is highly desirable.

Table 2 - Area under the receiver operating characteristics curves (AUC) and sensitivities at fixed specificities for the volumetric crowding index (VCI) and the volumetric apical crowding index (VACI). Sensitivity, specificity, likelihood ratio (LR) and accuracy are presented for the best cutoff values of VCI and VACI.

Parameter	AUC (SE)	Sensitivity/specificity		Cutoff value	Sensitivity/specificity at cutoff value	LR (95% CI)	Accuracy (95% CI)
		Specificity $\geq$ 95%	Specificity $\geq$ 80%				
VCI	0.86 (0.04)	56/95	71/80	1.08	71%/80%	3.6 (2.1–6.2)	76% (67%–85%)
VACI	0.92 (0.31)	66/95	93/80	4.14	90%/87%	6.9 (3.9–10.8)	88% (80%–93%)

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Figure 3 - A, B and C. Examples of the area outlined on 3 coronal slices of computed tomography scans, from which measurements were obtained. Representation of the soft tissue (mostly muscles) (D) and orbital fat (E) apical volumes based on sequential coronal orbital slices.

Previous CT studies have demonstrated a direct correlation between orbital apex crowding by enlarged extraocular muscles and the development of DON (6,12,13,18,24,25). Recent studies also suggest that bony orbit anatomy may play an important role in the development of DON because narrow orbits are more susceptible to apex crowding (11). In addition, other CT features (such as intracranial fat prolapse, lacrimal gland displacement, exophthalmos severity and superior ophthalmic vein dilatation) have been proposed but have not been confirmed as useful for detecting DON (4,6,11,17,24,26).

Because the presence of apical crowding on CT imaging is strongly correlated with DON in GO, several authors have proposed indexes for detecting DON. Barret et al. (13) calculated a linear muscle index from CT images and found it to be reproducible and reasonably efficient for detecting DON. In a previous study, we investigated the sensitivity and specificity of this muscle index calculation with MDCT and found the best combination (79% sensitivity and 72% specificity) at a muscle index of 60% (5). Nugent et al. (14) proposed a categorical scale for apical crowding, which was later reproduced by many other authors (4,11,16,17). Using this method, Nugent et al. (14) found severe apical orbital crowding in 12 out of 18 orbits with DON, but only in 16 out of 124 orbits without DON. While it seems clear that crowding scores are useful for detecting DON, the accurate use of the scores is difficult because the authors of these studies did not provide clear definitions of the positions along the orbit where the coronal plan was used to determine their scores.

In our study, we attempted to improve on existing CT indexes with a volumetric quantification of orbital crowding. In previous studies, extraocular muscle volume estimates were useful for detecting DON, but the manual quantitative analysis of the extraocular measurements was time-consuming and complex (12,18,25). In our study, orbital structures could be precisely reformatted using an

MDCT scanner, and the measurement of the orbital structures with the volumetric analysis software was straightforward. The technology has mainly been used in studies to estimate the increase in orbital fat, the effect of orbital radiotherapy or the effect of orbital decompression on orbital structures. However, to our knowledge, no previous study has evaluated the technology's ability to predict DON (19,27-31). According to published guidelines for the radiologic measurement of tissue volumes in GO patients, there is currently no consensus on how to measure orbital fat and extraocular muscle volume (32). To obtain volume measurements, we used a computer-assisted algorithm based on the density of soft tissue and orbital fat. We then calculated the following two volumetric indexes: the VCI, which is the ratio of the extraocular muscle volume to the orbital fat volume and is based on axial scans of the entire orbit; and the VACI, which is the ratio of the extraocular muscle volume to the orbital fat volume and is based on coronal scans of the orbital apex. The indexes appeared to be reliable and reproducible, as suggested by the high ICC values found in this study.

In our study, all patients were carefully and prospectively evaluated for the presence or absence of DON, and a large number of orbits with optic neuropathy were included. Both indexes were efficient at differentiating patients with DON from patients without DON. The VACI, which evaluates the orbital apex, was particularly effective; it achieved a sensitivity of 90% and a specificity of 87% at a cutoff of 4.14, whereas the VCI achieved only 71% sensitivity and 80% specificity at a cutoff of 1.08. These findings indicate that volumetric orbital crowding measurements are better at detecting DON in patients with GO when they are restricted to the orbital apex.

Our analysis of the performance of the VACI indicates a significant improvement over previous indexes in identifying patients with DON. The VACI was more efficient than

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both the Nugent scale, which was evaluated in several previous studies (4,14,16,17), and the linear muscle index described by Barret et al. (13). The latter suggested that an index of 67% or greater would have a diagnostic sensitivity of 67% for detecting DON (13). In a previous study that investigated the sensitivity and specificity of this muscle index using MDCT, the best sensitivity/specificity combination (79%/72%) was observed at a muscle index of 60% (5). This is clearly inferior to the performance of the indexes tested in the current study.

In conclusion, our study tested the value of two volumetric indexes for assessing the degree of apical crowding, one based on measurements of the entire orbit and one based on measurements of the orbital apex only. Both indexes were found to be efficient at predicting DON, although the latter index was more effective. Further studies are necessary to validate our findings.

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AUTHOR CONTRIBUTIONS

Gonçalves ACP contributed to the project design, data collection, data management, and writing the manuscript. Silva LN designed the project and collected data. Gebim EMM designed the project, collected data and revised the manuscript. Matayoshi S designed the project and revised the manuscript. Monteiro ML designed the project, analyzed data, and wrote and revised the manuscript.

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6 COMENTÁRIOS CONCLUSIVOS

A NOD é uma grave complicação da OG que ocorre em aproximadamente 4 a 8% dos pacientes.^(19, 20) Seu diagnóstico baseia-se em exames clínicos como os de acuidade visual, das reações pupilares, do fundo de olho, campo visual, potencial visual evocado e da visão de cores. Entretanto, esse diagnóstico clínico é frequentemente duvidoso. Desse modo, exames complementares de imagem capazes de auxiliar na detecção da NOD são muito importantes. Utilizamos a TC, um exame de fácil acesso em nosso meio e comum na prática clínica, para estudar métodos objetivos com essa finalidade.

O mecanismo fisiopatológico da NOD mais aceito é o da compressão do nervo óptico no ápice orbitário pelos músculos extraoculares aumentados. Vários estudos documentaram a relação entre a NOD e o preenchimento do ápice orbitário pelos músculos extraoculares utilizando medidas na TC.^(21, 26, 29, 31, 32, 37, 41)

Com base nesse conceito, procuramos revalidar índices quantitativos do preenchimento muscular do ápice orbitário previamente descritos, assim como calcular novos índices e avaliar a capacidade deles em detectar a NOD.

Os resultados deste estudo possibilitaram as seguintes conclusões:

1. Revalidamos o índice muscular de preenchimento orbitário descrito previamente por Barret e colaboradores⁽³²⁾ com a TC de multidetectores. O índice calculado foi significativamente diferente entre os grupos com e sem NOD. A melhor combinação de especificidade e sensibilidade foi observada com o índice de 60% de ocupação muscular, apresentando

especificidade de 79%, sensibilidade de 72% e razão de chances 9,2 para a detecção da NOD. Pela praticidade de se calcular o índice de Barrett em pacientes com OG submetidos a TC de multidetectores, acreditamos que esse índice seja útil na triagem pelo radiologista de pacientes com grande probabilidade de apresentar a NOD;

2. Em nosso estudo, o índice subjetivo de graduação do preenchimento muscular do ápice orbitário descrito por Nugent e colaboradores ⁽³⁸⁾ apresentou, para a presença de grau 1 ou mais, sensibilidade de 58,3%, especificidade de 84,7%, acurácia de 63% e razão de chances de 2,2. Entretanto, em nosso estudo nenhuma órbita apresentou grau 3 de preenchimento muscular apical, diferentemente dos estudos prévios. ^(20, 21, 24, 30, 39) Acreditamos que essas diferenças decorrem da falta de uma clara definição do ponto no ápice orbitário onde é realizada a graduação, como também da subjetividade de graduação do método;
3. Os três índices de área de preenchimento muscular da órbita ineditamente calculados em nosso estudo apresentaram diferenças significantes entre os grupos de órbitas com e sem NOD. Dentre esses índices, a 12, 18 e 24 mm da linha interzigomática, o índice a 18 mm apresentou o melhor desempenho na detecção da NOD. Nele observamos sensibilidade de 91,7%, especificidade de 89,9%, acurácia de 90,5% e razão de chance de 97,2. Observamos, assim, que essa nova metodologia objetiva de quantificar o preenchimento muscular do ápice orbitário é mais eficiente que o método subjetivo de graduação de Nugent. Pela praticidade e possibilidade de ser calculada nas estações de trabalho dos TC de multidetectores, acreditamos

que os índices de área sejam úteis na triagem pelo radiologista de pacientes com grande probabilidade de apresentar a NOD, da mesma forma que o índice de Barrett, porém com uma maior eficácia. A reprodutibilidade dos índices de área foi analisada com o coeficiente de correlação intraclasse e apresentou excelente concordância;

4. Reproduzimos também o método descrito primeiramente por Birchall e colaboradores.⁽³⁹⁾ Com a utilização da TC de multidetectores, pudemos ser precisos na observação da herniação de gordura exatamente nos pontos referidos pelos autores. Entretanto, em desacordo com os resultados do artigo original, a presença de herniação de gordura pela fissura orbitária superior não apresentou diferença significativa entre os grupos. Assim como outros autores,^(24, 30) observamos que esse sinal não foi preditivo da NOD;
5. Realizamos medidas de volume em um programa específico da estação de trabalho da TC de multidetectores e calculamos dois índices: o primeiro baseado em medidas de toda a órbita e o segundo a partir de medidas da estruturas restritas ao ápice orbitário. Ambos os índices apresentaram diferenças significantes entre os grupos de órbitas com e sem NOD. Dentre os dois índices o segundo apresentou maior eficácia diagnóstica em detectar a NOD, com sensibilidade e especificidade de 92 e 86%, respectivamente. Esses achados indicam que medidas de preenchimento muscular da órbita são mais eficazes quando restritas ao ápice. A reprodutibilidade dos índices volumétricos também foi analisada com o coeficiente de correlação intraclasse e apresentou excelente concordância.

Nossos achados concordam com a hipótese de que o preenchimento muscular do ápice orbitário é o principal fator causal da patogênese da NOD. O desenho prospectivo de nosso estudo, aliado à facilidade e precisão técnica de trabalhar com imagens na estação de trabalho dos tomógrafos de multidetectores, conferiu grande confiabilidade e reprodutibilidade aos nossos achados. A continuidade dos estudos na busca de métodos objetivos e capazes de identificar a neuropatia óptica distireoidiana com cada vez maior eficiência e praticidade é de grande relevância para a melhoria do diagnóstico e do tratamento da OG e de sua principal complicação, a NOD.

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