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CANADIAN JOURNAL OF OPTOMETRY | REVUE CANADIENNE D'OPTOMÉTRIE

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REFINING DECISIONS ON WHICH PRIMARY CARE PATIENTS TO SCREEN FOR GLAUCOMA

NUTRITION & BEHAVIOR

PART THREE / SPECIFIC NUTRIENTS AND THEIR RELEVANCE TO DISEASE

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CORRECTION

Apologies to our CAO Past-President. Dr Len Koltun's name was mispelled in the August issue.

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CONNECTING VISIONS

A New Stategic Plan for CAO

by KIRSTEN NORTH, OD, PRESIDENT CAO

In 2005, the CAO Council approved a four year Strategic Plan for CAO that included several key strategic directions in the following areas: Government Policy and Legislation; Standard of Care for Canadians, Stakeholder Influence, Public Education and Internal Infrastructure/Governance. Strategic actions and objectives were established in each area. To maintain consistency, we restructured CAO's organizational structure to reflect the strategic plan. CAO Council also organized its meeting agendas in the same way.

For the past four years, CAO Council tracked the progress on the strategic actions. At every council and executive committee meeting an updated report was circulated and reviewed. In addition, CAO members heard about strategic activities at provincial Annual General Meetings, CAO General Business Meetings and in the Canadian Journal of Optometry. At the recent CAO Congress, outgoing President, Dr. Len Koltun took pride in reporting that, on average, CAO had implemented close to 80% of its strategic plan.

As the new CAO President, I wanted to renew the CAO strategic plan as soon as possible and we held a special council planning session on October 16-17. We even used the same facilitator that we did in 2005. Most of the strategic directions will be retained; we focused our energies on updating the actions, objectives and accountabilities for the next four years.

The planning session also included a full day review of CAO communications/branding strategies. This session was in response to an independent audit of our current communications/branding programs that were completed in 2008. CAO Council considered whether our national television advertising program continues to be justified and effective and how does the CAO and the profession build upon that significant investment? How do we communicate with other markets beyond the core target market for the television campaign (female head of household)? How do we maximize our public relations efforts beyond Eye Health Month? How do we build our 'brand' for the benefit of CAO members and the public?

The review of communications/branding also involved seeking feedback of members, provincial associations and other stakeholders.

I look forward to having a clear CAO strategic plan to guide me during my presidency. In an upcoming issue of CJO we will publish the new plan for the benefit of all CAO members.

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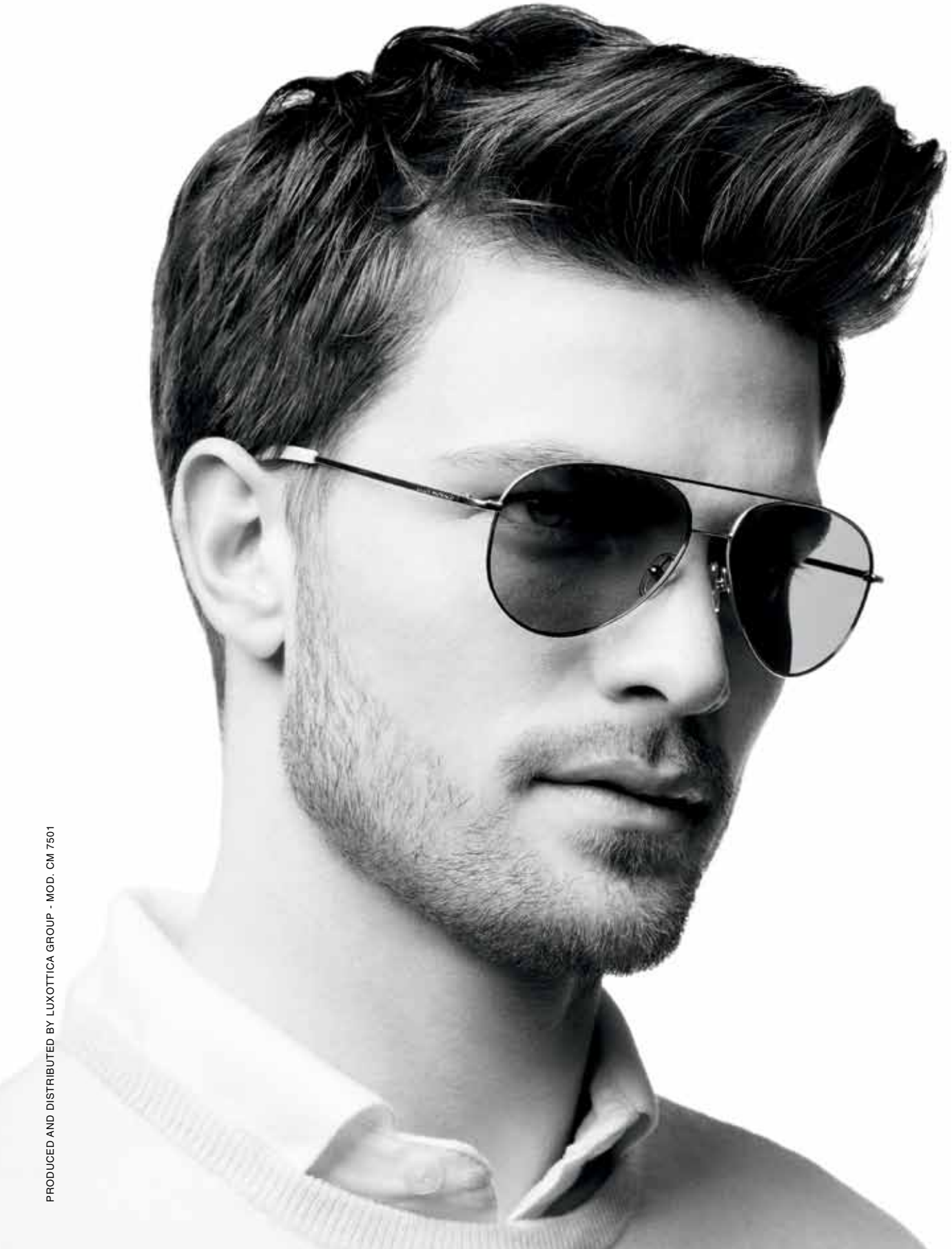

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Hiring in the Optometric Practice
Trouver des employés pour son cabinet optométrique

by / par ALPHONSE CAREW, OD

The optometric practice needs to be a truly customer, or patient, focused organization in order to become the practice we wish it to be. Nothing impacts our patient's perception of our office more than their experience with your staff, for they generally spend far more time with them than they do you! It is vitally important that you attract the right kind of new hires and train these people in an efficient manner.

Because of growth, or due to someone leaving, the process starts with the search for a new person. You should seek out the newer web-based services for your posting as most people now view these as their main place to look for jobs, the newspaper ad is only useful in small markets where it still has a loyal readership. Spell out as best you can what you are looking for, provide a short job description, the general location of the practice along with the office hours and expected salary range. It's best to be as clear as possible so that those who respond will be highly matched to what you need.

Once the resumes are whittled down to a few good candidates these should be interviewed at your office, with at least two people sitting in on the interview. It's a good idea to have a staff member who will be working with the new hire as the second person. There are plenty of on-line resources that can provide questions to ask but in general you are looking for someone who is capable of learning and has a pleasant demeanour, how they answer questions is more important than their actual answer. Can they think quickly on their feet? Do they have a friendly, warm manner? It is better to hire for personality and aptitude as these people can be trained for nearly any position.

Once you have found the right person and they have accepted the position with your terms (including a three month probationary period) the training period starts. It is of the utmost importance to get this person started with the right attitude, you don't get a second chance of making that first and lasting impression. On their first day set aside 20 or 30 minutes to explain the culture, mission and values of your practice. For the rest of the day have them shadow one of your staff who is doing the job that he, or she, will be

doing. There maybe some procedures you wish to teach to the new hire yourself, but most can be trained by an existing staff member. Make sure you choose an employee who is expert at what they do and has the desire and ability to teach someone, for not everyone is good at this.

There are also on-line resources to provide your new staff with background information on what an optometric practice does, along with the various roles inside the office. CAO has a great optometric assistance course that they offer by correspondence, we make the course mandatory for every employee once they have gone through their probationary period.

It is important to follow-up on the new hire on a regular basis. Meet with the person regularly to see how they are fitting in as well as how their training is going. I like to use a printed spreadsheet that lists the tasks that the person has to learn how to do and both the trainer and the supervising doctor has to sign off on each task once the person can demonstrate their mastery of the procedure. We have these spreadsheets for various positions in our office, once it is developed it only takes a little effort to keep it up to date. By the time of the 3 month review the candidate should have their spreadsheet tasks completed and is fitting in nicely, if there is anything lacking we will usually either extend the probationary period or decide to let the person go and start again. It's better to be sure you have the right person for the job tather than forcing the fit or making allowances.

Today's workers become terribly frustrated when they are thrown into a job with little or no training and it greatly increases the chances of them walking away from your office. It can be expensive, in both money and time, to replace these staff members so it is important to seek out the right candidate, follow-up with them regularly and train them to be experts.

Le cabinet optométrique doit véritablement être orienté vers le client ou le patient si nous voulons qu'il devienne le cabinet que nous souhaitons. Rien n'influence plus la perception que nos patients se font de notre bureau que les relations qu'ils entretiennent avec vos employés, car ils passeront habituellement beaucoup plus de temps avec eux qu'avec vous! Il est donc essentiel que vous attiriez les bons employés et que vous les formiez efficacement.

Que ce soit parce que votre cabinet a pris de l'expansion ou parce qu'un employé a quitté son emploi, le processus commence par une recherche. Pourquoi ne pas envoyer votre demande de personnel aux nouveaux services d'emploi sur Internet, que la plupart des gens aujourd'hui consultent au premier rang? Une annonce de journal n'est efficace que dans un marché restreint où le journal compte encore un lectorat fidèle. Soyez aussi précis et aussi clair que possible dans ce que vous cherchez : courte description du poste, emplacement général du cabinet, heures de travail et échelle salariale. Vous aurez ainsi plus de chance d'attirer des personnes qui correspondent exactement à vos critères.

Dès que vous aurez sélectionné les meilleurs candidats parmi les curriculum vitæ que vous aurez reçus, conviez-les à une entrevue à votre cabinet, à laquelle participera au moins une autre personne. Il serait bon que cette deuxième personne soit un membre du personnel qui travaillera avec le nouvel employé. Il y a une multitude de ressources en ligne qui peuvent vous fournir des questions à poser, mais vous cherchez en général quelqu'un capable d'apprendre et affichant une attitude plaisante. La façon de répondre est plus importante que la réponse elle-même. La personne peut-elle réfléchir rapidement par elle-même? A-t-elle une attitude amicale et chaleureuse? Il est préférable d'embaucher une personne pour sa personnalité et ses aptitudes puisque vous pourrez ensuite la former pour à peu près n'importe quel travail.

Dès que vous aurez trouvé la bonne personne et qu'elle aura accepté le poste aux conditions que vous

lui offrez (dont une période de stage de trois mois), la période de formation débutera. Il est de la plus haute importance que cette personne commence avec la bonne attitude, puisqu'on n'a habituellement pas une deuxième chance de faire une première impression durable. Lors de la première journée de travail, prenez une trentaine de minutes pour expliquer la culture, la mission et les valeurs de votre cabinet. Pour le reste de la journée, demandez-lui d'observer un des employés dont il fera le travail. Vous désirerez peut-être enseigner vous-même quelques procédures à cette nouvelle personne, mais la plupart peuvent être formées par un membre du personnel existant. Choisissez comme formateur un employé qui connaît à fond son travail et qui a la capacité et le désir de transmettre ses connaissances, car tous n'excellent pas à enseigner.

Vous pouvez aussi trouver en ligne, pour votre nouvel employé, des renseignements de base sur les fonctions d'un cabinet d'optométrie et sur les divers rôles qu'on y joue. L'ACO offre un excellent cours par correspondance pour les assistants optométriques. Le cours devient obligatoire pour tous les employés à la fin de leur période de stage.

Il est important de faire un suivi régulier auprès de la nouvelle personne pour voir comment elle s'intègre et assimile la formation. J'aime utiliser un document écrit qui présente, à la façon d'un chiffrier, les tâches que la personne doit apprendre. Dès qu'elle démontre sa maîtrise d'une procédure, le formateur et l'optométriste signent la feuille en regard de la tâche en question. Nous disposons de feuilles de ce genre pour les postes de notre cabinet. Elles sont très faciles à tenir à jour. Au bout de la période de trois mois, le candidat devrait être confirmé dans sa maîtrise de chacune des tâches et il devrait s'être intégré parfaitement dans le cabinet. S'il reste des lacunes, nous prolongeons habituellement la période de stage ou nous donnons à la personne son congé et nous recommençons le processus d'embauche. Il est préférable d'avoir la bonne personne plutôt que d'essayer de forcer quelqu'un à s'intégrer dans un emploi ou de faire des compromis.

Aujourd'hui, il est terriblement frustrant pour un travailleur d'être catapulté dans un emploi sans aucune formation, d'autant plus que vous courez le risque qu'il quitte votre cabinet. Comme le remplacement des membres du personnel peut être un processus long et coûteux, il est important de trouver les bonnes personnes, d'assurer des suivis réguliers et de les former pour qu'elles deviennent des spécialistes dans leur travail.

Nutrition and Behavior as it Applies to Systemic and Ocular Disease 2009

Specific Nutrients and Their Relevance to Disease

BY LARRY J. ALEXANDER, OD, FAAO

Constituents of a Diet that Support Healthy Systemic and Ocular Function

Vitamin C

Linus Pauling brought Vitamin C to the forefront of healthcare by advocating mega-doses of Vitamin C to fight colds and minimize the risk of cancer. Even recently studies continue to corroborate his presumptions. The new information relates that the group most prone to enjoy the benefits of Vitamin C for the common cold are those individuals under heavy short-term physical stress. [280] Vitamin C is a water-soluble antioxidant working in concert with Vitamin E. Vitamin C must be obtained from the diet with absence creating the disease, scurvy. Early symptoms of scurvy include fatigue resulting from lowered levels of carnitine and norepinephrine.[281]

Vitamin C (Ascorbic Acid) is required for collagen synthesis, the synthesis of norepinephrine, carnitine and the conversion of cholesterol to bile acids. The overwhelming fame of Vitamin C is associated with its role as an antioxidant for the protection of molecules from damage by free radicals and reactive oxygen species (ROS) created during metabolism and toxin exposure such as smoking which creates oxidative stress.

IOP can be reduced by increasing concentrations of absorbate in the aqueous humor. This can be done by supplementing with vitamin C (0.5 gm/kg body weight). The IOP-lowering actions of vitamin C occur by improving collagen formation, increasing blood osmolarity, improving aqueous outflow, inhibiting lipid peroxidation and raising glutathione levels.[282-284] Vitamin C is known as a very active antioxidant that also creates an increase in Immunoglobulin A (IgA) and Immunoglobulin M (IgM) within the framework of the immune system.

There is the suggestion that vitamin supplementation suppresses leukocyte adhesion and thus endothelial dysfunction, associated with increase in iris blood flow perfusion in diabetes. It has also been suggested that the antioxidant vitamin C may be a therapeutic agent for preventing diabetic retinopathy. [285] Diabetes mellitus is associated with increased oxidative stress. One study suggests that supplementation with antioxidant vitamins C and E probably plays an important role in improving the constitution of the ocular surface in the patient with diabetes.[286] Plasma vitamin C levels are inversely associated with the risk for type 2 diabetes. There is an inverse association between fruit and vegetable intake and the risk for type 2 diabetes, with a greater effect for fruit intake.[287] Regarding Vitamin C as a part of an anti-Age Related Macular Degeneration formula, it has been shown that blue light could induce DNA damage to RPE cells but vitamin C could protect the RPE cells from the blue light-induced DNA damage.[288] Regarding anterior segment, the addition of ascorbic acid to the irrigation solution reduced the amount of endothelial cell loss during phacoemulsification by approximately 70%.[289] Likewise a significantly reduced mean level of ascorbic acid was observed in the aqueous humor of patients with exfoliation syndrome in one study. In view of the fact that ascorbic acid is a major protective factor against free radical action, a role for free radical action is suggested as a possible factor in the genesis of exfoliation syndrome.[290]

The utilization of Vitamin C for the prevention of cataract has long been in the literature. While studies continue to be controversial one

study showed the risk for cataract is 60% lower among persons who use multivitamins or any supplement containing vitamin C or E for more than 10 years. However the use of vitamins for shorter duration is not associated with reduced risk for cataract.[291] Another study demonstrated that Vitamin C reduced the risk of cortical cataracts in women aged 60 years or less and carotenoids reduce the risk of posterior subcapsular cataract in women who have never smoked.[292] Research by the Nutrition and Vision Project (NVP), a cooperative effort of Harvard and Tufts University scientists, has found that women who consume higher-than-recommended doses of vitamin C may lower their risk for more than one type of cataract.[293]

Immune system activities of Vitamin C are extensive. Vitamin C enhances prostaglandin E1 (PGE1) and thus assists in the regulation of T cell function. Vitamin C increases killer T cell activity and B cell function. It also increases glutathione levels. It is known to protect against viruses by strengthening connective tissue and neutralizing toxins released by phagocytes. The RDA for Vitamin C is 100 to 125 mg/day. The tolerable upper level for vitamin C is established at 2000 mg/day. [294] Daily supplementation of vitamin C is recommended with consideration for the increased risk for kidney stones. [295] Recommended levels vary considerably with the sources and care should be exercised when evaluating these variables.

Potential harms of all variations of high-dose antioxidant supplementation must be considered. These may include an increased risk of lung cancer in smokers (beta-carotene), kidney stones, heart failure in people with vascular disease or diabetes (vitamin E) and hospitalization for genitourinary conditions (zinc).

Vitamin D

Vitamin D is a fat-soluble vitamin (in actual fact a steroid hormone) essential for promoting calcium absorption in the gut and maintaining adequate serum calcium and phosphate concentrations to enable normal mineralization of bone and to prevent hypocalcemic tetany. It is also needed for bone growth and bone remodeling.[296] Severe Vitamin D deficiency in infants and children results in rickets with growth plate enlarging without the support of mineralization of the long bones. This results in bowing. Vitamin D3 (cholecalciferol) can be synthesized by humans in the skin upon exposure to ultraviolet-B (UVB) radiation. It can also be obtained from the diet, but is fat-soluble. Sufficient vitamin D prevents rickets in children and osteomalacia in adults and, together with calcium, vitamin D helps protect older adults from osteoporosis. A quantitative meta-analysis recently concluded that at a mean daily dose of vitamin D of 528 IU there was a significant decrease in death (7% to 8%) for those using vitamin D supplement. [297]

It has been estimated that 50% to 60% of people do not have satisfactory vitamin-D status, likely related to urbanization, demographic shifts, decreased outdoor activity, air pollution and global dimming, as well as decreases in the cutaneous production of vitamin D with age. One prospective cohort study demonstrates for the first time that low 25-hydroxyvitamin-D and 1,25-dihydroxyvitamin-D levels are associated with increased risk in all-cause and cardiovascular mortality compared with patients with higher serum vitamin-D levels.[298-300] Another recent study found that 40.7% of patients with chronic migraine were deficient in 25-hydroxyvitamin D. The study also showed that the longer individuals had chronic migraine, the more likely they were to be vitamin D deficient. [301]

Vitamin D deficiency is widespread among patients being treated for osteoporosis, and such deficiency should be treated aggressively.[302] Recent reports have increased the awareness of a much broader role for vitamin D. Vitamin D is involved in differentiation of tissues during development and in proper functioning of the immune system. Over 900 different genes are now known to be able to bind the vitamin D receptor, through which vitamin D mediates its effects. The majority of effects of vitamin D in the body are related to the activity of 1,25(OH)2D including 50 specific genes. 1,25(OH)2D also inhibits proliferation and stimulates differentiation of cells as well as having activity as an immune

system modulator. It is even suggested that 1,25(OH)2D may enhance innate immunity and protect against many autoimmune disorders.[303-304] Evidence also continues to accumulate suggesting a beneficial role for vitamin D in protecting against autoimmune diseases, including multiple sclerosis and type I diabetes, as well as some forms of cancer, particularly colorectal and breast.[305-306] Most biological effects of Vitamin D are mediated through a nuclear transcription factor VDR.[307-309] A recent article concludes that there is ample biological evidence to suggest an important role for vitamin D in brain development and function, and that supplementation for groups chronically low in vitamin D is warranted. Since Calcium is so linked to neurodegeneration, one may hypothesize a link between Vitamin D, the immune system and the negative actions of the calcium ion.[310]

Hypovitaminosis D, especially at levels less than 30 ng/mL, is associated with an increased risk for Myocardial Infarct in men. Vitamin D is likely to exert its effect on the risk for cardiovascular disease via vascular smooth muscle cell proliferation, inflammation, vascular calcification, the renin-angiotensin system, and blood pressure.[311-312] The rate of cardiovascular disease–related deaths is greater at higher latitudes, lower at higher altitudes, and higher in the winter months — all associations related to vitamin D deficiency. The vitamin D axis affects vascular smooth muscle cell proliferation, inflammation, vascular calcification, the renin-angiotensin system, and blood pressure, all of which affect cardiovascular disease and MI risk, but evidence linking hypovitaminosis D and MI is sparse. Current recommendations for vitamin D are 200 to 600 IU per day, which may be inadequate to prevent cardiovascular disease. Another recent study demonstrated that use of calcitriol in patients with stage III or IV Chronic Kidney Disease (CKD) with hyperparathyroidism is associated with reduced risk for mortality and long-term dialysis and that the use of calcitriol in patients with stage III or IV CKD with hyperparathyroidism is associated with increased risk for hypercalcemia. CKD affects more than 10% of the US population with disturbances in vitamin D and mineral metabolism. [313]

For the first time Vitamin D deficiency has been linked to a poorer outcome in breast cancer.[314] Risk factors for Vitamin D deficiency include: dark skin, sunscreens, clothing covering the majority of the skin, increasing age, gastrointestinal disorders associated with fat malabsorption, obesity, bariatric surgery, ill-advised dieting, and a poor diet. The results of most clinical trials suggest that vitamin D supplementation can slow bone density losses or decrease the risk of osteoporotic fracture in men and women.[315-318] but the issue is still very controversial. Indeed, vitamin D3 (cholecalciferol) is now known to be greater than three times more potent than vitamin D2.[319-320] In order for vitamin D supplementation to be effective in preserving bone health, adequate dietary calcium (1,000 to 1,200 mg/day) should also be consumed. In general adults should take a supplement that supplies 400IU of vitamin D3 daily and should have 10-15 minutes of sun exposure at least three times a week as close to noon as possible. Should sunlight exposure be unattainable, 800IU of D3 is advised. In reality it is best to aim for serum levels of 80 nmol/L to minimize risk of disease. Toxicity-hypercalcemia can lead to bone loss, kidney stones, and calcification of the heart and kidneys. Because the consequences of hypervitaminosis D and ensuing hypercalcemia are severe, the Food and Nutrition Board established a very conservative upper limit of 2,000 IU/day (50 mcg/day) for children and adults 321 while other reports suggest 10,000IU is tolerated.[322-323]

A recent study, while equating low vitamin D levels to an increased risk of mortality, concludes that they would not advise people to take supplements without knowing their vitamin-D levels and that the most sensible advice for those wanting to ensure their levels remain optimal is to spend 10 to 15 minutes per day in the sun and to eat vitamin-D-fortified foods, such as milk and oily fish.[324]

More recent studies relate the importance of Vitamin D3 to the eyes. Based on encouraging preliminary findings, more study is recommended on the benefit of antioxidant supplements for age-related macular degeneration and of selenium for cancer prevention. In contrast to the state of the art for antioxidant supplements, there is strong and

Simplifying Presbyopic Contact Lens Fitting

Vishakha Thakrar
Johnson & Johnson Vision Care
Professional Affairs Consultant

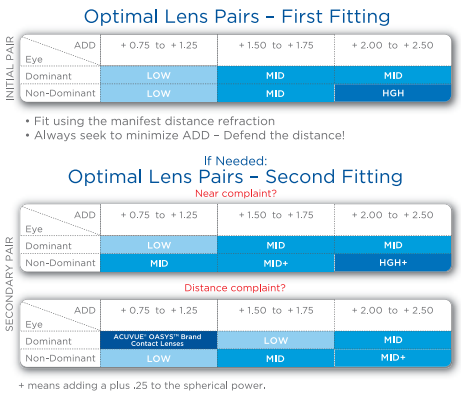
We are experiencing an explosion in the number of presbyopes in Canada. How many of us embrace contact lenses as an option for these patients? Our experiences have taught us that multifocal lenses are too time consuming, presbyopes are not comfortable in contact lenses, and glasses are easier. Obviously it's understandable if we hesitate to consider multifocal contacts.

Johnson & Johnson Vision Care recently launched the newest lens in the ACUVUE® OASYS™ Brand family, ACUVUE® OASYS™ Brand Contact Lenses *for PRESBYOPIA* to help us seize the opportunity in front of us every day. The lens incorporates STEREO PRECISION TECHNOLOGY™, a unique lens design that's taken 10 years of research to develop. This innovative design incorporates concentric zones with varying degrees of asphericity, also called a zonal asphere, and features a back-surface asphere for centration. This is completely different from its predecessor, ACUVUE® *BIFOCAL*. It uses the eye's natural depth of focus to provide balanced distance, intermediate and near vision in both light and dim illumination. I traditionally have used older aspheric designs and had some success, but the challenge that I dealt with was the change in vision with changes in illumination. This revolutionary new design tackles this problem.

How to fit the lens

I cannot emphasize enough how important it is to use the STEREO PRECISION SELECT™ tool (Figure 1) to find the best possible lenses. This clinically tested, proprietary tool enables quick and easy fitting. The most successful practitioners to fit ACUVUE® OASYS™ *for PRESBYOPIA* follow this guide rather than deviating and attempting to fit it "their own way". Multifocal lenses have been challenging to fit in the past, so many of us incorporated our own methods of fitting. FITTING YOUR OWN WAY DOES NOT WORK WITH THESE LENSES. Clinical studies have shown that by following the STEREO PRECISION SELECT™ tool, fit success is 70-80% by the second visit. This means less chair time. Previous multifocal designs have never offered that kind of success. No wonder so many practitioners would shy away from using multifocal lenses.

Figure 1



Who to target?

Success with ACUVUE® OASYS™ *for PRESBYOPIA* is much greater when you target the right patient. Choose patients who are current contact lens wearers and are motivated to see well without the dependency on glasses. Do not select patients who have unrealistic expectations. Those people are better off in glasses. And finally, be sure to educate your patients that with these lenses they should be able to conduct approximately 80% of their activities. Once their expectations are realistic, they are ready to be fit.

New Parameters

On August 17, the full parameter range will be released (-9.00D to +6.00D in quarter steps, ADD powers of Low, Mid and High). Personally, I am thrilled because I have patients waiting for the expanded parameters to be fit into this lens. However, the truth is that most of my contact lens patients are myopic (approximately 85%). So if myopia is the biggest opportunity, why aren't we fitting myopes as frequently as hyperopes? The easy answer is hyperopes were much easier to please with contact lenses. But by mainly fitting hyperopes with multifocal lenses, we lose out on a huge opportunity within our practices. This new lens design helps reduce the distance compromises that myopes do not accept, making it easier to fit and satisfy the visual expectations of an emerging presbyope.

By the age of 50, 72% of our contact lens patients have dropped out of lens wear. ACUVUE® OASYS™ *for PRESBYOPIA*, with its innovative design and unsurpassed comfort, has the potential to keep these patients in contact lenses longer; therefore increasing the overall success of our practices.

V. Thakrar

Dr. Thakrar practices in Burlington, Ontario, and specializes in specialty and scleral contact lens fitting of patients with corneal and external ocular disease. She is also a consultant for Johnson & Johnson Vision Care.

compelling support for the health benefits of supplements of Vitamin D and calcium when intake/status of these nutrients is not optimal. Thus, specific recommendations for these supplements in older adults are warranted. [325] It has been shown that Levels of serum vitamin D were inversely associated with early AMD but not advanced AMD and that milk intake was inversely associated with early AMD. Coincidently fish intake was inversely associated with advanced AMD in this report. It was reported that consistent use vs nonuse of vitamin D from supplements was inversely associated with early AMD only in individuals who did not consume milk daily.[326] Carrying this one step further, it was found that Higher levels of Bone Mineral Density (BMD) may be associated with lower risk for ARM. The underlying mechanism is unknown, although BMD may be a marker for lifetime endogenous estrogen exposure.[327]

Vitamin D is present in only a few foods (e.g. fatty fish), and is also added to fortified milk, but our supply typically comes mostly from exposure to ultraviolet rays (UV) in sunlight. UV from the sun converts a biochemical in the skin to vitamin D, which is then metabolized to calcitriol, its active form and an important hormone. Formation of vitamin D by UV can be 6 times more efficient in light skin than dark skin, which is an important cause of the known widespread vitamin D deficiency among African Americans living in northern latitudes. The issue of how Vitamin D relates to the general and ocular health of individuals is evolving with research outstripping one's ability to "keep up." A recent AARP magazine presented the following as cited by Michael F. Holick PhD, MD of the Vitamin D, Skin and Bone Research Laboratory of Boston University Medical Center.

"To get the vitamin D value of ten minutes' exposure to sunlight, you'd have to eat… 6 ½ pounds of shitake mushrooms or 150 egg yolks or 3 ¾ pounds of fresh farmed salmon or 30 servings of fortified cereal or 2 1/6 pounds of sardines or 30 cups of fortified orange juice." Do the calorie count on that exercise and realize that food sources of vitamin D actually complicate the issue.

Vitamin E

Alpha-tocopherol is the only form of Vitamin E in the human body and is the form recommended for supplementation. Vitamin E is the body's primary fat-soluble antioxidant and it must be obtained from food or supplements. As an antioxidant Alpha-tocopherol neutralizes free radicals then must be transformed back to Alpha-tocopherol with the assistance of other antioxidants such as Vitamin C. Vitamin E travels through the body in low-density liporoteins which protect them from from oxidation. Vitamin E is known to affect the expression and activity of immune and inflammatory cells, to enhance vasodilation and to inhibit the activity of the cell signaling molecule protein kinase C (PKC). Modulating the PKC

pathway may be relevant in glaucoma as PKC inhibitors relax the trabecular meshwork and affect matrix metalloproteinase and PGF2 alpha.[328] It has been shown that retinal vascular dysfunction due to hyperglycemia was prevented by vitamin E.[329] It has also been reported that vitamin E as d-alpha tocopheryl acetate in 300 to 600 mg/day dosages improved blood flow and reduced visual field change in glaucomatous eyes.[330]

Alpha-tocopherol at 400 to 800 IU per day is an effective antioxidant with fame in reducing the oxidation of low-density lipoproteins to prevent formation of foam cells and thus atherosclerotic plaques. Most interest in vitamin E surrounds the cardiovascular issue. While the studies are variable most point to the fact that vitamin E consumption is associated with some degree of risk reduction in cardiovascular disease with up to 90% of Americans not consuming the RDA of 15 mg/day. [331-334] Results of trials of intervention with vitamin E in vascular disease have been totally non-definitive. [335-337]

In the framework of diabetes, the studies are likewise inconsistent and contradictory.[338-340] One study does however state that oral vitamin E treatment appears to be effective in normalizing retinal hemodynamic abnormalities and improving renal function in type 1 diabetic patients of short disease duration without inducing a significant change in glycemic control. This suggests that vitamin E supplementation may provide an additional benefit in reducing the risks for developing diabetic retinopathy or nephropathy.[341]

Data from the NHANES 1999-2000 indicate that mean dietary intake of alpha-tocopherol is 6.3 mg/day and 7.8 mg/day for women and men, respectively.[342-342] These intakes are well below the current intake recommendations of 15 mg/day. As previously stated it is estimated that more than 90% of Americans do not meet daily dietary recommendations for vitamin E.[344]

Alpha-tocopherol has been shown to enhance the immune system. Additionally, it works synergistically with Omega 3 Fatty Acids to protect cells from tumor necrosis factor alpha (TNF-a) induced apoptosis. Supplementation with Vitamin E has also been shown to increase B cell activity in the aging patient. [345-346] Vitamin E also works synergistically with Vitamin C to reduce inflammatory prostaglandins and increase T cells, IL-2 and tumor necrosis factor beta (TNF-B).

In a prospective observational data from a large cohort of female health professionals, higher dietary intakes of lutein/zeaxanthin and vitamin E from food and supplements were associated with significantly decreased risks of cataract. [347] Of interest, a recent study points to the fact that results demonstrated that there was no significant difference between the 600 mg vitamin E and placebo groups in the incidence of cataract when vitamin E was the only intervention.[348] While this might surprise some, nutrition and health are a combination of many elements. In the realm of ARMD, one study showed evidence that antioxidant (beta-carotene, vitamin C, and vitamin E) and zinc supplementation slowed down the progression to advanced AMD and visual acuity loss in people with signs of the disease, but no evidence that vitamin E or beta-carotene prevented AMD. [349-351] Health is not a single item but rather a cornucopia of actions and these two contradictory studies point to that.

Upper levels for safety of consumption of vitamin E are established by the Food and Nutrition Board of the Institute of Medicine to minimize hemorrahage for alpha-tocopherol supplements are 1,000 mg/day of alpha-tocopherol in any form (equivalent to 1,500 IU/day of RRR-alpha-tocopherol or 1,100 IU/day of all-rac-alpha-tocopherol). One meta-analysis reported that to reduce the risk of any disease that 2000 IU/day were necessary to reduce the risk by 6%.[352] Other studies found no evidence of the decrease of the risk of death with vitamin E supplementation.[353-355]

Drug interactions must be taken into account realizing that hemorrhage at excessive dosages is a potential issue. Any pharmaceutical agents, foods or supplements such as gingko biloba should raise the caution of interaction.

Scientists at the Linus Pauling Institute in Oregon feel there exists credible evidence that taking a supplement of 200 IU (134 mg) of natural source d-alpha-tocopherol

(RRR-alpha-tocopherol) daily with a meal may help protect adults from chronic diseases, such as heart disease, stroke, neurodegenerative diseases, and some types of cancer. The amount of alpha-tocopherol required for such beneficial effects appears to be much greater than that which could be achieved through diet alone. ((lpi.oregonstate.edu) Controversy reigns with recommendations on Vitamin E and any dosages beyond RDA should be carefully considered in view of other health and nutritional issues.

Natural sources of alpha-tocopherol include olive oil, sunflower oil, nuts, whole grains , green leafy vegetables but usually provide less than the RDA of 15 mg/day of RRR-alpha-tocopherol.[356] Supplements made from entirely natural sources contain only RRR-alpha-tocopherol (also labeled d-alpha-tocopherol). RRR-alpha-tocopherol is the isomer preferred for use by the body, making it the most bioavailable form of alpha-tocopherol. Synthetic alpha-tocopherol is less bioavailable and only half as potent. The formulas for conversion to the RRR form are:

- RRR-alpha-tocopherol (natural or d-alpha-tocopherol):
- IU x 0.67 = mg RRR-alpha-tocopherol
- all-rac-alpha-tocopherol (synthetic or dl-alpha-tocopherol):
- IU x 0.45 = mg RRR-alpha-tocopherol.

Lutein/Zeaxanthin

The yellow color of the macula lutea is due to the presence of the carotenoid pigments lutein and zeaxanthin. In contrast to human blood and tissues, no other major carotenoids including Beta-carotene or lycopene are found in this tissue.[357] The associations between MP density and serum lutein, serum zeaxanthin, and adipose lutein concentrations are stronger in men than in women.[358]

A number of studies intended to examine trends in a population suggest a link between increased lutein and decreased risk of eye disease:

In 1994, a National Eye Institute (NEI)-supported study indicated that consumption of foods rich in carotenoids — particularly green, leafy vegetables such as collard greens, kale, and spinach — was associated with a reduced risk of developing macular degeneration.[359]

In 1999, data from the Nurses Health Study showed a reduced likelihood of cataract surgery with increasing intakes of lutein and another carotenoid — zeaxanthin. [360]

In 1999, the Health Professionals Follow-up Study found a trend toward a lower risk of cataract extraction with higher intakes of lutein and zeaxanthin. [361]

In 1999, a follow-up to an NEI-supported population-based study — called the Beaver Dam Study — concluded that people with diets higher in lutein and zeaxanthin had a lower risk of developing cataract. [362]

In 2001, data from the Third National Health and Nutrition Examination Survey reported that higher intakes of lutein and zeaxanthin among people ages 40-59 may be associated with a reduced risk of advanced AMD. [363]

Conversely, in 1998, the Beaver Dam Study found no significant association between the risk of either early or advanced AMD in groups that had either the highest intakes of lutein and zeaxanthin or the lowest intakes of lutein and zeaxanthin. The study researchers caution that generally, the consumption of lutein and zeaxanthin in this population may have been too low to have had an impact on the risk of AMD. [364-365]

In the 2004 LAST (Lutein Antioxidant Supplement Trial) study, 90 AMD patients were supplemented daily with an OcuPower supplement capsule containing 10 mg of crystalline FloraGLO lutein, 10 mg lutein plus a mixed antioxidant formula, or placebo for 12 months. The average American ingests one to two mg of lutein daily. Patients ingesting the lutein supplement experienced significant improvements in several objective measurements of visual function including glare recovery, contrast sensitivity, and visual acuity vs. placebo. Patients also experienced a 50% increase in macular pigment density relative to those on placebo.[366]

In the 2007 LAST study it was found that individuals with the lowest Macular Pigment Optical Density (MPOD) and in greatest need of supplementation, were also likely to benefit from lutein or the lutein plus antioxidant.[367]

Another study evaluated a total of 1802 women from ages 50 to 79. These women were described as having dietary and serum levels of lutein and zeaxanthin either above the 78th (high) or below the 28th

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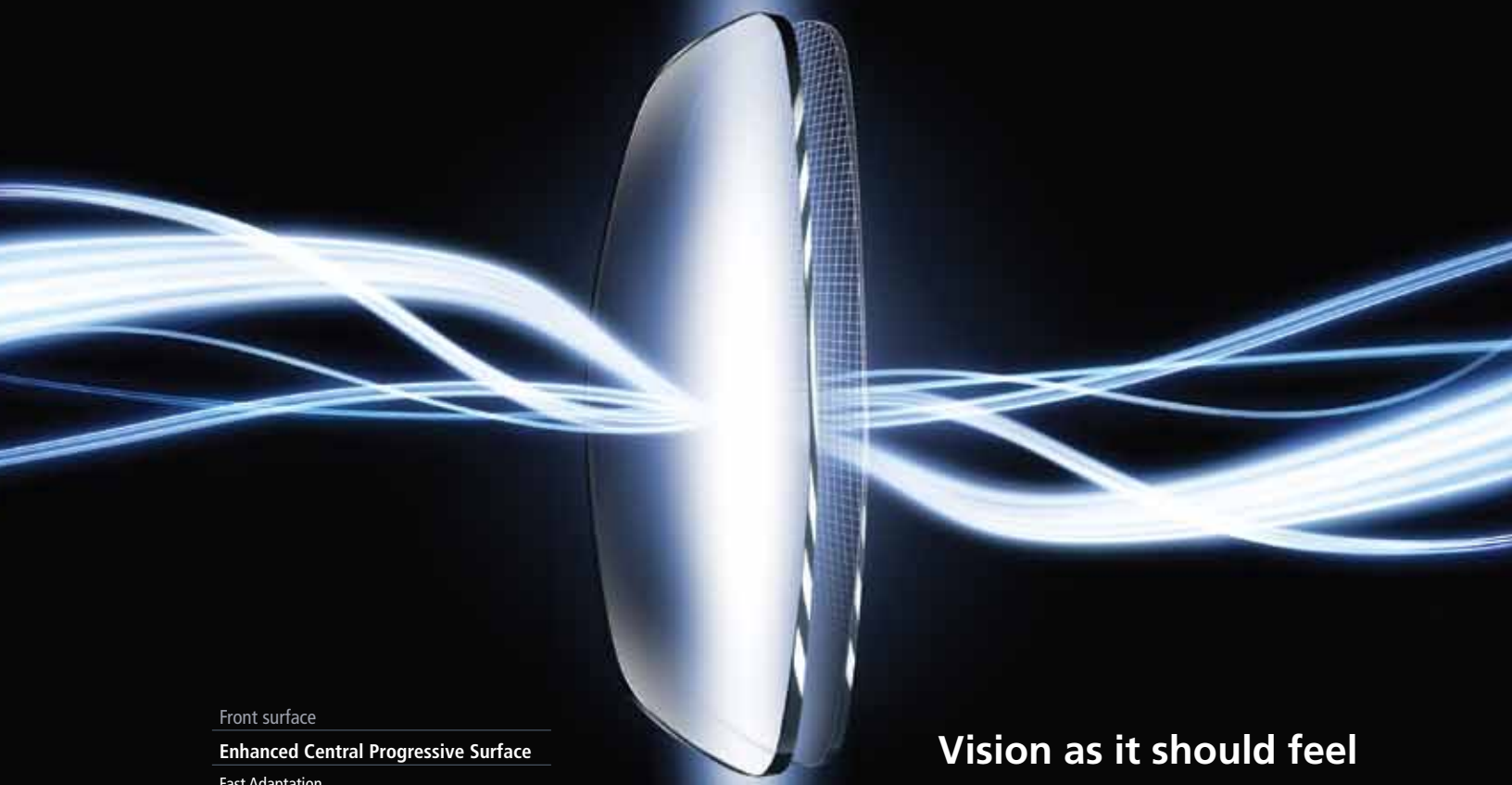

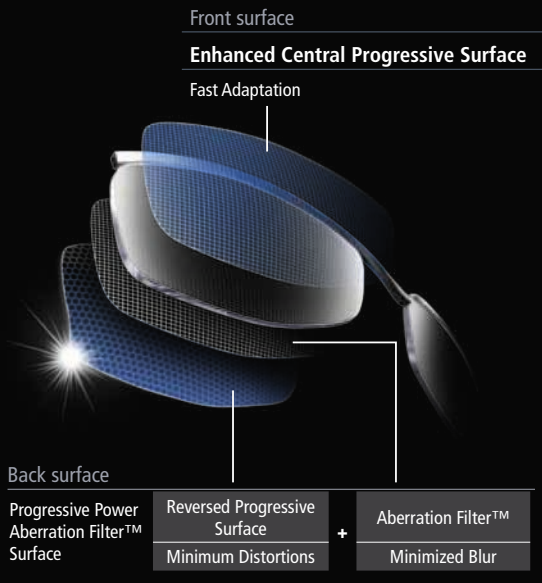

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(low) percentile. The prevalence of nuclear cataract was 23% lower in the high-diet group compared with the low-diet group. Furthermore, those in the highest quintile were 32% less likely to have a nuclear cataract compared with the lowest quintile. [368]

Higher dietary intake of lutein/zeaxanthin was independently associated with decreased likelihood of having neovascular AMD, geographic atrophy, and large or extensive intermediate drusen.[369-370] In non-advanced AMD eyes, a selective dysfunction in the central retina (0 degrees – 5 degrees) can be improved by the supplementation with carotenoids and antioxidants. No functional changes are present in the more peripheral (5 degrees – 20 degrees) retinal areas.[371] It has been shown that the synergistic action of zeaxanthin and vitamin E or C found in one study demonstrates the importance of the antioxidant interaction in efficient protection of cell membranes against oxidative damage induced by photosensitized reactions.[372]

One report suggests that lutein and zeaxanthin (the only carotenoids found in the lens) may retard aging of the lens.[373] Another reports that observations indicate dietary modulation of diabetic retinopathy risk may be possible by increasing intakes of lutein and lycopene-rich foods.[374] While the studies continue to be both prolific and very controversial very interesting conclusions have been drawn in juxtaposition. On the basis of one evidence-based review, the FDA concluded that no credible evidence exists for a health claim about the intake of lutein or zeaxanthin (or both) and the risk of age-related macular degeneration or cataracts.[375] Another study states that a higher dietary intake of lutein/zeaxanthin was independently associated with decreased likelihood of having neovascular AMD, geographic atrophy, and large or extensive intermediate drusen.[376] A contrary study found only alpha-tocopherol and beta-cryptoxanthin were related to late AMD as single antioxidants. On the other hand, the carotene and carotenoid families as a combination of antioxidants were protectively associated with late AMD. No relationship was found between serum antioxidants and early AMD. Our findings support the hypothesis that a combination of serum antioxidants obtained from the traditional Japanese diet is protective for late AMD, but not for early AMD.[377] Further controversy continues with finding stating that persons with intermediate age-related macular degeneration or advanced age-related macular degeneration (neovascular or central geographic atrophy) in one eye should consider taking the AREDS-type supplements. Further evaluation of nutritional factors, specifically, lutein/zeaxanthin and omega-3 fatty acids will be tested in a multicenter controlled, randomized trial — the Age-Related Eye Disease Study 2 (AREDS2).[378]

No one can even accurately estimate the RDA of Lutein. One study cites the fact that macular concentration of lutein and zeaxantin decreases with age, what exacerbates harmful effect of blue light on photoreceptors. Lutein and zeaxantin act as a filter of the high energy blue light. Besides, these carotenoids are strong antioxidants and neutralize light-generated free radicals. Plant foods are the exclusive dietary sources of the carotenoids. Their average intake in the European countries is several times lower than 6 mg daily, which is the estimated recommended intake.[379] One study is bold enough to say that elderly human subjects with and without AMD can safely take supplements of lutein up to 10 mg/d for 6 months with no apparent toxicity or side effects.[380]

One study covers the ground pretty well stating that observational and clinical trials support the safety of higher intakes of the phytochemicals lutein and zeaxanthin and their association with reducing risks of cataracts in healthy postmenopausal women and improving clinical features of AMD in patients. Additional phytochemicals of emerging interest, like green tea catechins, anthocyanins, resveratrol, and Ginkgo biloba, shown to ameliorate ocular oxidative stress, deserve more attention in future clinical trials. Obtuse, yet obtuse.[381] Yet another spin, The carotenoid zeaxanthin accumulates in the human macula lutea and protects retinal cells from blue light damage.

Thus, consumption of zeaxanthin-rich potatoes significantly increases chylomicron zeaxanthin concentrations suggesting that potentially such potatoes could be used as an important dietary source of

zeaxanthin.[382] Another study chimes in with the assessment that after multivariate adjustment for potential confounders 1980 energy-adjusted intakes of alpha-carotene, beta-carotene, lycopene, total retinol, total vitamin A, and total vitamin E were significantly inversely related to the prevalence of pigmentary abnormalities (PA). Furthermore, increasing frequency of consuming foods high in alpha-or beta-carotene was associated with lower odds of Pigmentary Abnormalities. Alluding to the impact of multiple antioxidants on ARMD.[383]

Another interesting historical twist has presented in the nutritional arena as related to lutein. One report states that concentrations of serum lutein 26% and zeaxanthin 38% increased after 5-wk of 1 egg/d compared with the phase prior to consuming eggs. Serum concentrations of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were not affected. These findings indicate that in older adults, 5 wk of consuming 1 egg/d significantly increases serum lutein and zeaxanthin concentrations without elevating serum lipids and lipoprotein cholesterol concentrations.[384] Another report goes on to say for these reasons, dietary recommendations aimed at restricting egg consumption should not be generalized to include all individuals (70% of the population experiences a mild increase or no alterations in plasma cholesterol concentrations when challenged with high amounts of dietary cholesterol (hyporesponders). It appears that diverse healthy populations experience no risk in developing coronary heart disease by increasing their intake of cholesterol but, in contrast, they may have multiple beneficial effects by the inclusion of eggs in their regular diet.[385] In regard to the potential negative cardiovascular risk other studies suggest as well a potential contribution of lutein and zeaxanthin to the prevention of heart disease and stroke. It is worth noting that recommendations to consume foods rich in xanthophylls are consistent with current dietary guidelines. Lutein and zeaxanthin are xanthophyll carotenoids found particularly in dark-green leafy vegetables and in egg yolks. They are widely distributed in tissues and are the principal carotenoids in most tissue throughout the body.[386-387] In conclusion, the lutein bioavailability from egg is higher than that from other sources such as lutein, lutein ester supplements, and spinach.[388]

The most provocative information to come along in a while is the relationship of Omega 3 fatty acids to the entire process of macular degeneration, ocular disease and systemic disorders. While these are not covered in detail here, it is important to understand the concept of inflammation and how it contributes to ARMD and ocular disorders. One study's objective was to determine the effects of lutein (12 mg/d) and DHA (800 mg/d) on their serum concentrations and macular pigment optical density (MPOD) Lutein supplementation increased MPOD eccentrically. DHA resulted in central increases. These results may be due to changes in lipoproteins. Lutein and DHA may aid in prevention of age-related macular degeneration.[389] Another study corroborates the fact that n-3 Fatty acids, particularly docosahexaenoic acid (DHA), are highly concentrated in brain and retinal tissue and may prevent or delay the progression of dementia and AMD. Low dietary intakes and plasma concentrations have been reported to be associated with dementia, cognitive decline, and AMD risk. They go on to reports that their own unpublished observations from the Framingham Heart Study suggest that > or =180 mg/d of dietary DHA (approximately 2.7 fish servings/wk) is associated with an approximately 50% reduction in dementia risk. At least this amount of DHA is generally found in one commercially available 1-g fish oil capsule given daily.[390] Further information regarding inflammation and AMD demonstrated that Linolenic acid was positively associated with risk of AMD docosahexaenoic acid (DHA) had a modest inverse relation with AMD and that >4 servings of fish/wk was associated with a 35% lower risk of AMD compared with < or = 3 servings/mo. Also total fat intake was positively associated with risk of AMD. The conclusion was a high intake of fish may reduce the risk of AMD.[391] Likewise higher levels of serum antioxidants vitamin C and lutein/zeaxanthin and higher fish intake were associated with lower serum C-Reactive Protein (CRP) levels, whereas serum vitamin E, smoking, and increased body mass index

were associated with increased CRP. Furthermore, serum vitamin E, serum alpha-carotene, and dietary intake of antioxidants and vitamin B6 were associated with lower levels of plasma HCY, whereas hypertension was associated with increased HCY. C-reactive protein and HCY levels are related to traditional dietary and behavioral factors associated with age-related macular degeneration. [392] One more study corroborates the relationship stating that a higher frequency of fish consumption was associated with decreased odds of late ARM. Subjects with higher energy-adjusted intakes of cholesterol were significantly more likely to have late ARM. The amount and type of dietary fat intake may be associated with ARM.[393]

With review of the issues of lutein, ambiguity reigns. One report advocates that vitamins C and E, and lutein/zeaxanthin should be included in our theoretically ideal ocular nutritional supplement.[394] Another understates saying that until scientifically sound knowledge is available we recommend for patients judged to be at risk for AMD to: alter their diet to more dark green leafy vegetables, wear UV protective lenses and a hat when outdoors. [395] Lutein and zeaxanthin do not exist in a vacuum and the entire issue of health is multifactorial. Diet looms as critically important in the genesis of all disease and AMD is not an exception. An illustration of that is the fact that high consumption of corn bread indicated significant association with central vision loss (OR 0.4; 95% CI 0.2, 0.9)in 168 rural elders.[396] This relates to the fact that cross-sectional studies indicate that diets that provide a higher dietary glycemic index (dGI) are associated with a greater risk of age-related macular degeneration (AMD). Persons at risk of AMD progression, especially those at high risk of advanced AMD, may benefit from consuming a smaller amount of refined carbohydrates.[397] The association between dietary glycemic index (dGI) and AMD from the AREDS cross-sectional analysis at baseline suggests that a reduction in the dGI, a modifiable risk factor, may provide a means of diminishing the risk of AMD.[398]

While Lutein and Zeaxanthin are readily available in dark leafy green vegetables, patients with concerns about blood clotting must avoid some of these because of the Vitamin K-clotting factor-in these vegetables. Lutein and Zeaxanthin may be supplemented in pill or egg form without fear of interference with blood thinners.

Glutathione

Glutathione is the most abundant antioxidant in the body, produced in the body, found in every cell in the body and is the primary free radical fighter. It is the regenerator of immune cells. It is produced in every cell with the help of selenium, magnesium and vitamin C. Glutathione production decreases with age. The pathway for collagen remodeling and apoptosis induction in glaucoma seems to be exogenously influenced by water-soluble antioxidants, for example, glutathione. The pathway for elastin remodelling and apoptosis induction seems to be influenced by endogenous lipid-soluble antioxidants, for example, vitamin E.[399] Supplementation with glutathione is not accomplished well orally and the utilization of supplementation is not well documented.

Magnesium

Magnesium is a mineral and is very short acting. The majority of magnesium is within the skeleton, with about 25% in muscle and it is involved in more than 300 essential reactions within the body.[400] Magnesium is involved in glutathione production, cell membrane genesis and chromosome activity. As related to cellular mechanism magnesium is critical in ions transport across cell membranes, as evident in the neurodegeneration model. Magnesium acts as a smooth muscle relaxant, partially inhibits the effect of endothelin (a vasoconstrictor), and is a calcium channel blocker, and as such often acts as a vasodilator and improves peripheral circulation.[401-404] Some studies suggest that magnesium plays a role in hypertension and cardiovascular disease but there is no definitive work to underscore the recommendations for intervention.[405-411] Magnesium is very involved in the ATP-synthesizing protein in mitiochondria and as such in the neuroprotection pathway. [412]

Magnesium seems to have a beneficial effect on the visual field in glaucoma patients with both increased and normal IOP — possibly by alleviating vasospasm at 300 mg/day. Magnesium also works to activate enzymatic

systems.[413-414] Magnesium does not directly influence immune function but rather is critical in 300 enzymatic functions in the body. Magnesium deficiency causes an increase in pro-inflammatory cytokines and an excess production of free radicals and as a result increases the effects of the inflammatory process.

Magnesium depletion is commonly associated with both insulin dependent (IDDM) and non-insulin dependent (NIDDM)diabetes mellitus. Between 25% and 38% of diabetics have been found to have decreased serum levels of magnesium (hypomagnesemia) perhaps associated with urinary issues.[415] It is suggested but not proven that magnesium supplementation may be beneficial in patients with diabetes.[416-417]

From a neurological standpoint, persons with recurrent migraines have lower magnesium levels.[418] Supplementation to alleviate the headaches has produced conflicting results and the levels of supplementation to achieve modulation of the headaches result in side effects.[419-420]

Magnesium absorption is impaired by a low protein diet, a high fiber diet, and excesses in zinc consumption, GI disorders, bariatric surgery renal disorders, chronic alcoholism, increasing age.[421] Magnesium can interact with digoxin, anti-malarials, some drugs to treat osteoporosis,, tranquilizers, oral anticoagulants and some antibiotics. In seriously ill patients, the primary care physician should be consulted.

Consumption of magnesium in the US is considered lower than the RDA. Natural sources of magnesium are cereals, brown rice, nuts, beans, spinach, chard, okra and bananas. Recommended daily dosage is 420 mg/day for men over 30 and 320 mg/day for women over 30 years of age. The recommended supplement is 100 mg/day assuming some dietary consumption of magnesium. The tolerable upper level of intake (UL), which is 350 mg/day set by the Food and Nutrition Board.[422]

Zinc

Zinc is an essential trace element for the proper functioning of a number of human systems. Zinc is critical for 100 different enzymes relevant to their catalytic role.[423] Zinc is also critical in the structure of proteins and cell membranes. Cell membranes are susceptible to oxidative damage with loss of zinc. [424] Zinc also has a role in gene expression acting in the role of transcription factors as well as having responsibilities in cell signaling. Zinc also plays a role in apoptosis.[425]

Zinc served the role as the entry point for eye care into the realization of the importance of nutrition in ocular health. Use in the management of macular degeneration has resulted in mixed reports. [426-432] The element is, however, a part of the AREDS recommendation. When speaking about commercially available vitamin supplements it should be noted that zinc at 80 mg/day resulted in increase genitourinary hospital admissions in the AREDS study.[433] It has also been found that based on the evidence it is suggest that zinc plays a role in sub-RPE deposit formation in the aging human eye and possibly also in the development and/or progression of AMD. [434]

Large quantities of zinc interfere with copper bioavailability by inducing intestinal sysnthesis of metallothionein, which traps copper.[435] This action may then lead to cupric anemia. Zinc consumption must be accompanied by copper supplementation. Iron supplementation and calcium combined with phytic acid (limes) may also decrease the availability of zinc.[436] Zinc is required for the enzyme that converts retinol (vitamin A) to retinal. Zinc deficiency is associated with decreased release of vitamin A from the liver, which may contribute to symptoms of night blindness that are seen with zinc deficiency.[437] High doses of zinc also impact negatively in the absorption of magnesium.[438]

Zinc is important in the immune system and has gained much press in regard to the prevention of colds and respiratory disease and gastrointestinal disorders especially as related to children.[439-443] There are also implications regarding diarrhea with The World Health Organization and the United Nations Children's Fund currently recommending zinc supplementation as part of the treatment for diarrheal diseases in young children.[444] A recent meta-analysis of published randomized controlled trials on the use of zinc gluconate lozenges in colds found that evidence for their effectiveness in reducing the duration of common colds was still lacking.[445] Use of intranasal zinc is also of questionable value.[446-447] with recent

removal from the market for loss of smell.[448]

Zinc picolinate has been promoted as a more absorbable form of zinc, but there are few data to support this idea in humans. In order to prevent copper deficiency, the U.S. Food and Nutrition Board set the tolerable upper level of intake (UL) for adults at 40 mg/day, including dietary and supplemental zinc.[449] Most AREDs formulas contain double that recommendation. The recommendation for zinc is to take a multivitamin supplement containing 100% of the daily values (DV) of most nutrients will generally provide 15 mg/day of zinc. Use of zinc may decrease the absorption of tetracyclines and quinolones so an interval of two hours is appropriate.[450]

Natural sources of zinc include crab, oysters, beef, pork, dark meat chicken and turkey, yogurt, cheese, milk, cashews, almonds, peanuts, and beans.

Zinc is critical in a number of different interactions in the body but in excess there may be danger both systemically and in the potentiation of ARMD.

Part 4 of this series will be a continuation of the discussion of the specific supplements and their benefits in the management of diseases and disorders. This will include an extensive discussion of the very timely issue of Omega 3 and Omega 6 fatty acids. It will be printed in Spring, 2010.

Dr. Alexander receives no reimbursement from any nutritional supply company. He is the Sr. Director of Clinical Education and Professional Relations for Optovue, Inc, a digital imaging company, which produces the RTVue and has a commitment to the visual well-being of the world.

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Refining decisions on which primary care patients to screen for glaucoma

BY BRUCE WICK, OD, PhD & RONALD GALL, OD, MSc

"It was the best of times. It was the worst of times." Charles Dickens classic opening to A Tale of Two Cites (1859) might well apply to today's glaucoma patient. On one hand, with today's exquisitely-accurate diagnostic instruments and new management procedures, diagnosis is easier and treatment is better than ever before. On the other hand, up to 50% of current patients with glaucoma do not know they have the disease[1] and many practitioners continue to use an intraocular pressure (IOP) and cup-to-disc (C/D) ratio approach to diagnosis.[2] However, some researchers are working with a systems-approach to help clinicians face the difficult task of deciding what action (risk assessment, follow closely, or consider therapy) to take for patients who may have open-angle glaucoma with only subtle signs of damage.[3]

In this paper, we address the issue of refining decisions of which primary care patients to screen for glaucoma. Using currently available instrumentation and clinical research, we provide normative data on specific physical ocular structures resulting in an extension for primary care examination that promises more accurate identification of which primary eye care patients should be screened for glaucoma, bringing more patients with glaucoma closer to "the best of times".

With introduction of the ophthalmoscope (1854), glaucoma came to be defined as an ocular disease characterized by optic nerve damage with associated elevated intraocular pressure.[4,5,6] Glaucoma is now considered as a group of ocular diseases, often accompanied by elevated intraocular pressure, that cause progressive optic nerve atrophy and blindness.[7] In most

ABSTRACT

INTRODUCTION: Glaucoma, which is often accompanied by elevated intraocular pressure (IOP), causes progressive optic nerve atrophy and blindness. Among ocular structure parameters abnormalities in central corneal thickness (CCT), cup-to-disc (C/D) ratio, inter-eye C/D ratio asymmetry, optic disc area, and neuro-retinal rim area (N-RRA) appear to be highly correlated with glaucoma. We compare these specific ocular structures in a group of young normal pre-presbyopic patients and in a group of patients being treated for glaucoma.

METHODS: After written informed consent, 1433 consecutive normal, and 56 consecutive patients being treated for glaucoma were assessed by including age, race, sex, IOP (NCT), C/D ratio, optic disc area, N-RRA (Optos), central center thickness (CCT), and anterior chamber depth.

RESULTS: Combinations of findings in CCT, C/D ratio, C/D ratio asymmetry, disc area, and N-RRA (assessed by Z-score) were present in 65.52% of patients being treated for glaucoma and 22.96% of young normal patients. For young normal patients, overall average CCT was 550.37+/-39.47µm. Overall average C/D ratio was 0.39+/-0.11. Inter-eye C/D asymmetry was 0.02+/-0.06. Overall average disc area was 2.46+/-0.49mm^2 (7863.54+/-1630.42 pixels). Overall average N-RRA was 1.44+/-0.35mm^2 (4785.88+/-1161.14 pixels). C/D ratio increased modestly with disc area increase, an increase not associated with thinning N-RRA. Thin N-RRA was associated with small optic discs that had large C/D (t=-8.21, p=0.000, DF=93). There was a significant difference between young normal patients and patients being treated for glaucoma in CCT, C/D ratio, C/D ratio asymmetry, disc area, and N-RRA.

CONCLUSION: More than one in five (22.96%) young normal patients has ocular structure findings similar to those found in patients being treated for glaucoma. These results will help refine decisions on which primary eye care patient to screen for glaucoma.

Key Words : corneal thickness, C/D ratio, optic disc area, neuro-retinal rim area, glaucoma screening

primary open angle glaucoma cases, high IOP damages the optic nerve causing nerve fiber layer loss that corresponds to a visual field deficit. Other than high IOP, risk factors associated with glaucoma include a large C/D ratio, C/D asymmetry, small neuro-retinal rim area, large optic disc area, and a thin central corneal thickness.

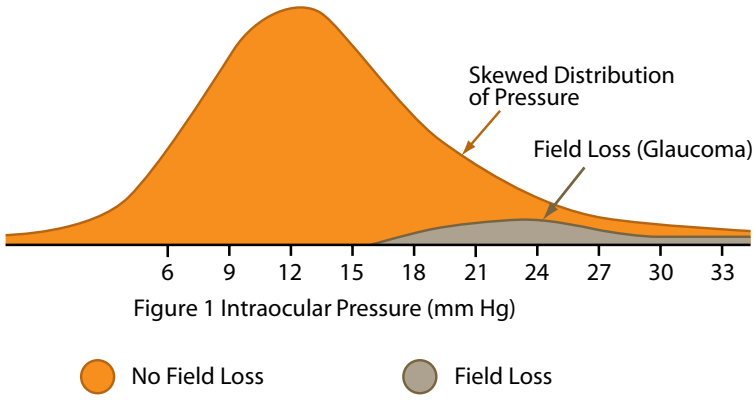

Figure 1: *In this diagram of intraocular pressure distribution there is a visible skew toward higher pressures (exaggerated slightly compared to the actual distribution). The average pressure among those with glaucomatous visual field loss is in the low 20s, even though glaucoma is not present in most individuals with similar pressures. And, although it is not common, some individuals with pressures in the upper teens have glaucomatous visual field loss.*

Intraocular Pressure

Intraocular pressure is the fluid pressure in the eye measured in millimeters of mercury. The normal range for intraocular pressure (IOP) is 10–20 mm Hg, with a mean of 15.5 mm Hg.[8] This pressure is maintained throughout life and between the sexes, although there is diurnal and possibly also some seasonal variation.[9] The IOP distribution in the general population is not a normal gaussian distribution, but is skewed toward higher pressures where an associated increase in visual field loss is often present (*Figure 1*).[10]

In general, the level of intraocular pressure is directly related to the probability of glaucomatous visual field loss. In a population based prevalence survey of more than 5000 individuals aged 40 and over[11], participants who had a screening intraocular pressure greater than 30 mm Hg were over 38 times more likely to have glaucoma (as defined in the study) than individuals with an intraocular pressure below 15 mm Hg. In the Blue Mountains Eye Study the odds of developing glaucoma were 4 to 7 times higher when the screening intraocular pressure was greater than 21 mm Hg than when there were lower intraocular pressures.[12] In addition, the chance of developing glaucoma is 2 to 8 times higher in patients with intraocular pressure asymmetry between eyes greater than 3 mm of Hg than in patients with smaller or no intraocular pressure asymmetry.[13]

Optic Nerve

The optic nerve (Cranial Nerve II) is collection of nerve fibers that carry visual information from the retina to the brain. Significantly increased IOP causes progressive optic nerve damage, which manifests as a loss of nerve axons accompanied by a characteristic progressive visual field loss.[14] The loss of axons gradually becomes visible clinically as an increase in optic nerve cupping.[15] As a result, one of the most frequent structural observations in patients suspected of having glaucoma is of the optic nerve: historically, assessment of the cup-to-disc (C/D) ratio is considered to be among the most important observations that can be used to detect glaucoma.

Cup-to-Disc Ratio (C/D)

C/D ratio is the relative comparison of the diameter of the cup to the diaeter of the optic nerve head. A large C/D ratio is considered a risk factor for glaucoma.[16] An early study of cup-to-disc ratios indicated that only 7% of the normal population had C/D ratios of 0.5 or greater and that 86% of normal C/D ratios were less than 0.4.[17] Because of this study, anyone with a C/D ratio greater than 0.4 was automatically considered a glaucoma suspect. More recent data on 4877 normal individuals suggest

that, in order to be considered abnormal, C/D ratios must be greater than 0.74 horizontally and 0.64 vertically.[18]

Cup-to-Disc (C/D) Ratio Asymmetry

Cup-to-disc (C/D) ratio asymmetry is the difference in the C/D ratio between the two eyes. Chi et al[19] found that inter-eye asymmetry of greater than 0.2 for the horizontal optic disc C/D ratio was present less than 10% of the time. These results have been taken to suggest that, in the presence of approximately symmetrical optic disc area, inter-eye C/D ratio asymmetry greater than 0.2 should raise the suspicion of glaucoma.

Other Glaucoma-related Ocular Structures

Notwithstanding the importance of the C/D ratio and inter-eye C/D ratio asymmetry, recent clinical research has identified ocular structures known to change in patients with glaucoma (neuro-retinal rim area[20]) or related to glaucoma (increased optic disc area[19] and decreased central corneal thickness [CCT]).[21]

Neuro-retinal Rim Area (N-RRA)

Neuro-retinal rim area (N-RRA) is the total disc area less the area of the cup (C/D ratio × Disc area). Of the parameters of the ONH, neuro-retinal rim area (N-RRA) appears to be most highly correlated with glaucomatous damage.[20] For example, on the Heidelberg Retinal Tomograph (HRT) N-RRA is an important piece of information in addition to the computer-derived cup shape measure.[22] Previous studies have demonstrated that optic discs with larger over-all areas have larger neuro-retinal rim areas compared to smaller optic discs.[23] The N-RRA appears to be an important clinical parameter for clinicians to evaluate when looking for and monitoring glaucoma, making estimation of the N-RRA an essential part of ONH examination.[24,25]

Optic Disc Area

Optic disc area is the surface area of the optic nerve head. The area of the disc varies from 0.92 to 5.54mm^2 in normal patients, with Black patients typically having a significantly larger disc areas than Caucasians.[26,27] Based on a study of a portion of the Ocular Hypertension Treatment Study (OHTS) participants, it has been suggested that patients with larger optic disc size may have an increased susceptibility to glaucoma.[28] In a larger disc there is more area for the nerve fibers to fill, allowing for a larger cup (although animal studies have demonstrated that nerves with larger over-all areas tend to have more nerve fibers when compared to nerves with small areas[29]). Since the area of the optic disc is large and less of it is occupied by the nerve fiber, the C/D ratio could be overestimated. An abnormal C/D ratio could occur with a normal optic disc area and a decrease in the number of nerve fibers leaving the eye (as occurs in glaucoma), or with an abnormally large optic disc area and a normal number of nerve fibers.

Central Corneal Thickness (CCT)

Central corneal thickness (CCT) is thickness in microns of the center of the cornea. The OHTS data document that a thin central cornea is associated with increased risk of glaucoma, irrespective of race.[28] The cause-and-effect relationship between central corneal thickness (CCT) and glaucoma is not yet clear. However, a patient with a thin cornea can have a falsely low IOP reading.

Research Question

Parameters of the CCT[28], C/D ratio[17,18], inter-eye C/D ratio asymmetry,[19], optic disc area[24,25], and N-RRA[20] have been investigated and compared for glaucoma patients and age matched normal subjects; C/D ratio[14,15] and C/D inter-eye asymmetry[19] have been evaluated for normal subjects. However, although the structures have been individually studied, multiple structure interrelationships have not been investigated in large numbers of normal subjects. Thus, what is not well delineated are the answers to our general research questions:

General Research Questions

1) Can decisions to determine which patients to screen for glaucoma be refined by determining the normal ranges of specific physical ocular structures?
2) And, can these normative data of specific physical ocular structures be applied to the age range of patients who participated to find those with anatomy similar to glaucoma patients?

The answers are important because only a small proportion of patients ever develop glaucoma; e.g., it is estimated that between 1.1% (11/1000 Caucasian) and 8.8% (88/1000 Black) of today's young adults will ultimately develop glaucoma[30], and up to 50% of current patients with glaucoma do not know they have the disease.[1]

The challenge presented is to investigate in both normal and glaucoma patients, using screening devices available in a routine clinical care setting, and various ocular structural factors (CCT, C/D ratio, inter eye C/D ratio asymmetry, optic disc area, and N-RRA) associated with glaucoma. The approach is relating normal and glaucoma specific physical ocular structures to each other; either gold standard testing (e.g., Goldmann tonometry for IOP, Stereo optic nerve photos for C/D evaluation) or screening devices available in routine clinical care (e.g. NCT for IOP, Optos for C/D evaluation), may be used as long as decisions are based on consistent equipment and resulting normative data.

Taken together, answers to our specific research question:

Specific Research Question

- Are there clinically significant numbers of healthy pre-presbyopic patients and patients being treated for glaucoma who have similar specific physical ocular structure relationship?

and our research objective:

Research Objective

- To provide data for young normal patients, gathered using screening devices available in a routine clinical setting, which delineate the normal range of specific physical ocular structures (CCT, C/D ratio, inter eye C/D ratio asymmetry, optic disc area, and N-RRA) as well as the interrelation between structure findings —

will allow routine clinical measures to be utilized to refine decisions concerning which primary eye care patients to screen for glaucoma beyond the cup/disc (C/D) ratio and IOP approach .

Methods

A total of 1433 patients not previously known to have glaucoma were evaluated in two separate clinics located in Houston, Texas (USA) and Oakville, Ontario (Canada). An additional group, selected from the Houston site, included 56 consecutive patients who were being treated for either primary open angle or low pressure glaucoma.[a] After written informed consent was granted, data collected included each patient's age, race (by self-report), sex, date of birth, intraocular pressure (IOP-NCT), anterior chamber depth and angle (Pentacam), central corneal thickness (CCT), cup-to-disc ratio (C/D), C/D asymmetry, optic disc area, and neuro-retinal rim area (N-RRA). These data were specifically gathered using routinely available non-invasive clinical care techniques so that the results would be as applicable to other providers as possible (where possible routinely available care procedures were "standardized" to insure their accuracy and use by other providers in the future).

In Houston, consecutive patients were included from the date of study onset. In Oakville, patients were selected based on willingness to have Optos examination. Young normal patients were between ages 4 and 40 years. Patients excluded were aged 4 or less (due to the lack of cooperation) and over age 41 (who were more at risk for glaucoma due to their age). Data from a few patients were not included due to inability to procure accurate anterior segment assessment with Pentacam. Also excluded from the young normal group were patients with glaucoma (progressive visual field defects, visible optic disc damage, and/or progressive nerve fiber layer thinning) and those who had undergone Lasik or corneal transplant surgeries.

C/D, C/D Asymmetry, Disc Area, Neuro-Retinal Rim Area

Optos

Images of the retina were captured using the Optos P200 Device, a panoramic 200-degree non-mydriatic screening ophthalmoscope. This retinal image scanner uses red and green laser wavelengths to produce a digital, high resolution color picture which is displayed on a PC monitor. These two laser wavelengths penetrate the retinal structures to different depths, each providing information for interpretation and diagnosis. Panoramic 200-degree images can be viewed, enlarged, annotated, and separated into their color components.

Cup-to-disc ratio was assessed on the red free image using a computer generated tool supplied with the Optos software (V^2 Vantage 2.3.0.70). First, the margins of the cup were traced using the color contours and the bending of blood vessels as a guide. The same technique was used

to draw the disc margins. This procedure automatically calculated the C/D ratio. For each subject, the C/D asymmetry was calculated by taking the difference between the right and left eye C/D ratio.

Disc area was also determined using the Optos software. The margins of the disc were traced using the color contours as a guide. This procedure automatically calculates the disc area ratio in pixels. Neuroretinal rim area (N-RRA) was calculated by subtracting the area of the cup (C/D ratio × Disc area) from the total disc area.

Conversion from pixels to mm^2

Optical coherence tomography (OCT) is an imaging technique, analogous to ultrasound B scan, that provides cross-sectional images of the retina with micrometer-scale resolution. It provides cross-section morphological features of the optic disc and normal anatomic variations in retinal and retinal nerve fiber layer thickness with 10 micron depth resolution. To estimate disc area in mm^2, we collected data for 82 eyes (41 patients), first with Optos to determine disc area in pixels and then for the same patients with OCT to determine disc area in mm^2. By comparing Optos values for disc area (in pixels) and OCT values (in mm^2) for the same patients we developed a conversion factor from pixels to disc area (mm^2).

Central Corneal Thickness

In Houston, Pentacam (Occulus Pentacam – Belinea) was performed on every patient to determine central corneal thickness, anterior chamber depth, and the anterior chamber angle in degrees. Pentacam is an instrument that uses a rotating Scheimpflug camera to take multiple images of the anterior segment. The center of the cornea is very precisely measured with this rotational imaging process. Measurements take less than two seconds and minute eye movements are captured and simultaneously corrected. Images are computer analyzed to generate three dimensional images and calculate measurements of the eye. In addition to corneal thickness measurements, the Pentacam provides corneal topography measurement, AC depth, volume, and angle, and pupil diameter assessment. In Oakville, optical pachymetry utilizing OLCR (Optical Low Coherence Reflectometry) technology, with a Haag-Streit Slit lamp-mounted Pachymeter was performed to determine corneal thickness.

Power Calculation

The goal of statistical power analysis and sample size estimation techniques is to facilitate decisions of how large a sample is needed to enable statistical judgments that are accurate and reliable and how likely statistical tests will be to detect significant differences in a particular situation.[31] Power indicates the probability that a clinical trial will have a significant (positive) result; that is, have a p-value of less than the chosen significance level (e.g., 0.05). [31] For a 0.05 level of significance, the corresponding power level is 0.80. This probability is calculated under the assumption that the difference equals the minimal detectable difference. In clinical trials, the minimum detectable difference is the smallest difference that would be clinically important and biologically plausible.

For example, consider the C/D ratio; the minimal detectable difference or "smallest difference" between normal (0.3) and glaucoma (0.5) patients could be 0.2. To calculate the sample size needed for a power level of 0.8, it may be assumed that for each group (normal and glaucoma) there are equal standard deviations (+/-0.1), degrees of freedom (df =100) and sample sizes. In this example, the sample size calculation shows that fewer than twenty (n<20) subjects are needed for each group (control and glaucoma) to have the power for a significant difference (p-value less than 0.05). Thus, our sample size of 1377 young normal eyes and 112 eyes being treated for glaucoma gives us more than ample power to detect clinically significant differences in the parameters studied (C/D, C/D Asymmetry, Disc Area, Neuro-Retinal Rim Area, and Central Corneal Thickness).

Results

From our study design we had normative data on 1377 eyes of 702 young normal subjects (621 – normal IOP; 81 – high IOP [>21mmHg]) and 112 eyes of 56 patients being treated for glaucoma. Of the young normal subjects, 291 were male (average age 16.56+/-8.39, range 5-40) and 411 were female (average age 19.87+/-9.54, range 4-39). There were 199 Black (181 – normal IOP), 175 Caucasian (168 – normal IOP), 173 Hispanic (153 – normal IOP), 118 Other


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(Asians of Indian and Pakistan origin; 83 - normal IOP), and 37 Asian (Vietnamese and Chinese; 36 – normal IOP) patients. Of the patients being treated for glaucoma, 18 were male (average age 61.40+/-12.42, range 41-80) and 38 were female (average age 63.92+/-13.29, range 41-87). There were 20 Black, 10 Caucasian, 14 Hispanic, 9 Other (Asians of Indian and Pakistan origin), and 3 Asian (Vietnamese and Chinese) patients being treated for glaucoma.

Z-Scores

In statistics, a standard score (also called z-score or normal score) is a dimensionless quantity derived by subtracting the population mean from an individual (raw) score and then dividing the difference by the population standard deviation. Since the Z-Score is dimensionless, individual Z-Scores for CCT, C/D ratio, disc area, C/D ratio asymmetry, and N-RRA can be combined through addition into a total Z-Score to portray the ocular structure of young normal patients (*see Figure 2*). For our young normal population the mean total Z-Score was 0.00 (range -7.32 to +9.24), with an increasing plus number indicating increasing prevalence of ocular structures that have been associated with glaucoma (CCT, C/D ratio, disc area, C/D ratio asymmetry, and N-RRA). Again, for our young normal population, the standard deviation was 2.30; 77.04% of young normal patients had a Z-score less than 2.30, 22.96% of patients were more than 1SD greater than the mean, and 6.48% were more than 2SD greater than the mean. For the patients being treated for glaucoma, using individual structure Z-Scores derived from the ocular structure mean and standard deviation of young normal patients, the mean total Z-Score was 3.25 (range -2.09 to +11.30). A Z-Score >2.30 was present in 65.52% of patients being treated for glaucoma.

These results demonstrate a positive answer to our:

Specific Research Question: are there clinically significant numbers of healthy pre-presbyopic patients and patients being treated for glaucoma who have similar specific physical ocular structure relationship?

Z-scores >2.30 are present in 22.96% of young normal patients and 65.52% of patients being treated for glaucoma.

Notwithstanding the fact that 22.96% (more than one in five) of young patients had Z-scores within the range of those present in patients being treated for glaucoma, there are statistically significant differences between young normal patients and patients being treated for glaucoma. Using a two sample t-test

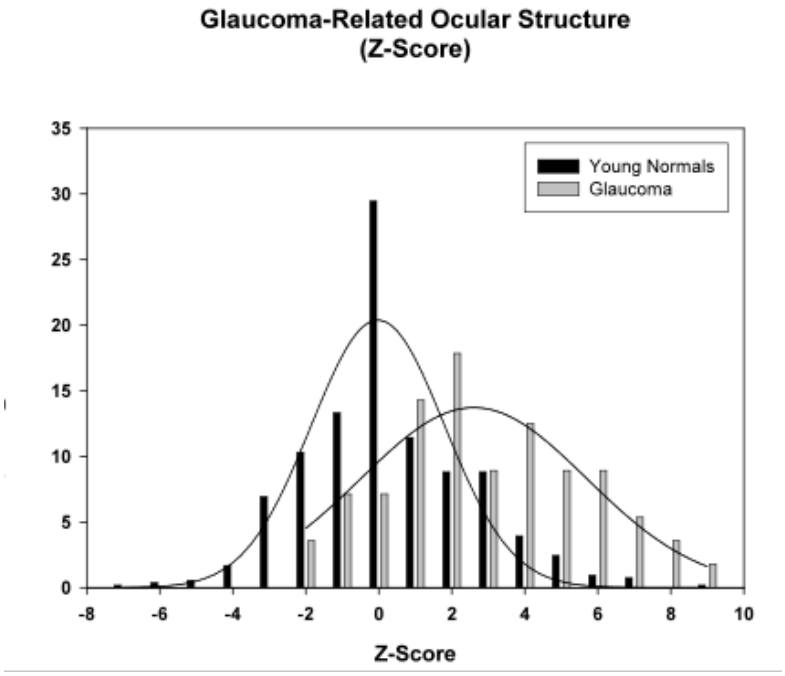

Figure 2: *For our young normal population the mean Z-Score was 0.00 (range -7.32 to +9.24), with an increasing plus number indicating an increasingly glaucoma-related structure. The standard deviation was 2.30; 77.04% of young normal patients had a Z-score less than 2.30. For the glaucoma patients, using a Z-Score derived from the ocular structure mean and standard deviation of young normals, the mean Z-Score was 3.25 (range -2.09 to +11.30). A Z-Score greater than 2.3 was present in 65.52% of glaucoma patients and 22.96% of young normal patients.*

(two-tailed, independent samples, unequal variance) for between-group differences, t-values were calculated, associated p-values estimated from a table[32], and degrees of freedom (df) assumed two less than the total number analyzed. The between-group difference of the young normal and patients being treated for glaucoma groups and its significance are shown in Table 1.

At the 0.05 level or higher:

- C/D ratio asymmetry of the patients being treated for glaucoma (0.08+/-0.12) was greater than the normal group (0.02+/-0.06).

At the 0.02 level or higher:

- Corneal thickness of the patients being treated for glaucoma (535.64+/-43.28) was thinner than the normal group (550.37+/-39.47). [b]

At the 0.01 level or higher:

- Disc area of the patients being treated for glaucoma (8626.01+/-2051.50) was larger than the normal group (7863.54+/-1630.42).

At the 0.001 level or higher:

- Age of the patients being treated for glaucoma (62.91+/-13.05) was higher than the normal group (19.09+/-9.40).
- C/D ratio of the patients being treated for glaucoma (0.57+/-0.09) was larger than the normal group (0.39+/-0.11).
- Neural-retina rim area (N-RRA) of the patients being treated for glaucoma (3593.30+/-922.30) was smaller than the normal group (4785.88+/-1161.14)

Data below elucidate our research objective.

Research Objective:

- To provide data for young normal patients, gathered using screening devices available in a routine clinical setting, which delineate the normal range of specific physical ocular structures (CCT, C/D ratio, inter eye C/D ratio asymmetry, optic disc area, and N-RRA) as well as the interrelation between structure findings.

Results for specific ocular structures of the 1377 eyes of young normal patients were as follows:

- central corneal thickness of 550.37+/-39.47mm.
- C/D ratio of 0.39+/-0.11
- between eye C/D ratio difference of 0.02+/-0.06
- disc area of 7863.54+/-1630.42 pixels
- N-RRA of 4785.88+/-1161.14 pixels

Data for each area assessed are presented in Table 2.

There were several parameters that were different in comparison of the various groups in the young normal cohort at a range of significance levels (*see Table 2*):

At the 0.01 level or higher:

- Female patients had thinner central corneal thickness (546.92+/-38.26mm) than male patients[b] (555.01+/-40.55mm).
- Caucasian patients had smaller disc areas (7392.73+/-1714.24) than the over-all study average (7863.54 +/-1630.42).

TABLE 1

GROUP COMPARISON

	Young Adult		Glaucoma		Group Comparison	
N=	Total	702	Total	56		
	Male	291	Male	18		
	Female	411	Female	38		
Eyes N=		1377		112		
	Mean	SD	Mean	SD	T-value	p-value
Age	19.09	9.40	62.91	13.05	24.55	<0.001
CCT	550.37	39.47	535.64	43.28	2.45	<0.02
C/D	0.39	0.11	0.57	0.09	13.58	<0.001
C/D Asymmetry	0.02	0.06	0.08	0.12	2.17	<0.05
Disc Area	7863.54	1630.42	8626.01	2051.50	2.71	<0.01
N-RRA	4785.88	1161.14	3593.30	922.30	9.10	<0.001

TABLE 2a

YOUNG ADULT DATA

Young Normal (IOP≤21)			High IOP* (IOP>21)		Asian (IOP≤21)		Black (IOP≤21)		Hispanic (IOP≤21)		Other (Pakistani & Indian Descent) (IOP≤21)		Caucasian (IOP≤21)	
N=	Total	621	Total	81	Total	36	Total	181	Total	153	Total	83	Total	168
	Male	260	Male	31	Male	19	Male	63	Male	72	Male	34	Male	72
	Female	361	Female	50	Female	17	Female	118	Female	81	Female	49	Female	96
Eyes N=		1377		134		72		362		306		166		336
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	19.09	9.40	13.63	5.52	21.28	9.96	19.03	9.56	17.59	8.90	16.82	8.33	21.18	9.62
IOP	15.68	2.92	22.48	3.13	15.09	2.61	15.66	2.93	16.23	2.81	15.99	2.99	15.13	2.98
CCT	550.37	39.47	583.75	42.49	550.64	34.59	533.36	37.81	560.61	39.85	553.25	37.45	553.51	39.20
C/D	0.39	0.11	0.41	0.11	0.43	0.11	0.41	0.11	0.39	0.11	0.40	0.12	0.34	0.10
C/D Asymmetry	0.02	0.06	0.02	0.05	0.0	0.05	0.02	0.06	0.02	0.06	0.02	0.07	0.01	0.04
AC Angle	37.45	11.99	37.49	9.98	34.71	6.26	37.95	7.36	38.32	17.66	35.83	6.50	37.11	6.91
AC/Depth	3.31	0.32	3.30	0.34	3.29	0.36	3.32	0.32	3.30	0.31	3.26	0.33	3.37	0.30
Disc Area	7863.54	1630.42	7579.55	1451.55	8319.47	1897.47	8003.52	1616.69	7976.01	1410.13	8099.01	1480.79	7392.73	1714.24
N-RRA	4785.88	1161.14	4338.79	845.64	4681.97	1143.41	4704.78	1044.42	4863.46	1057.86	4799.89	1106.60	4841.50	1379.51
N-RRA Asymmetry	119.50	677.05	107.41	599.85	61.29	486.74	124.82	626.66	118.14	759.08	45.62	703.58	208.68	644.06

*Included in the high IOP group are: 1 Asian, 18 Black, 20 Hispanic, 35 Other, and 7 Caucasian who are not included in the respective Ethnicity columns

TABLE 2B

T-TEST COMPARISON

Race	IOP	CCT	C/D	Angle	AC Depth	Disk Area	N-RRA
CxO	0.02		0.001		0.05	0.001	
CxH	0.001		0.001			0.01	
CxB		0.001	0.001			0.01	0.001
CxA			0.001	0.05		0.01	0.001
CxOverAll			0.001			0.01	
OxH							
OxB		0.001		0.02			
OxA							0.02
HxB		0.001					0.02
HxA	0.02		0.05	0.05			0.001
BxA		0.05		0.01			

*Caucasian smaller C/D; Caucasian smaller disk area; Black thinner cornea; Asian and black smaller N-RRA

HIGH IOP VS NORMAL IOP

IOP	CCT	C/D	Angle	AC Depth	Disk Area	N-RRA
	0.01	0.01			0.05	0.001
	Thicker	larger			Smaller	Smaller

*High IOP thicker cornea, larger C/D, smaller disk area, smaller N-RRA

At the 0.001 level or higher:

- Caucasian patients had smaller C/D ratios (0.34+/-0.1) than the over-all study average (0.39+/-0.11).
- Black patients had thinner central corneal thickness (533.36+/-37.81mm) than other groups (except Asians p=0.05).
- Asian (4681.97+/-1143.41) and Black (4704.78+/-1044.42) patients had smaller N-RRA than the N-RRA of Caucasian patients (4841.50+/-1379.51 pixels).

There were data on 134 eyes of 81 young normal patients with ocular hypertension (IOP >21, range 22-36). Their average age was 13.63+/-5.52, range 6-38. Compared to the over-all group, these patients also had differences at a range of significance levels:

At the 0.05 level or higher:

- Smaller disc area 7579.55+/-1451.55 pixels

At the 0.01 level or higher:

- Thicker cornea 583.75+/-42.29mm
- Larger C/D ratio 0.41+/-0.11

At the 0.001 level or higher:

- Smaller N-RRA 4338.79+/-845.64 pixels

For young-normal patients with thin N-RRA various relations were investigated:

- There was no relation to age (t=-0.04, p=0.966, df=98) – i.e., older patients were not more likely to have a thinner N-RRA.
- There was no relation to IOP (t=-1.00, p=0.320, df=91) – i.e., patients with higher IOP were not more likely to have a thinner N-RRA.
- There was no relation to corneal thickness (t=1.53 p=0.13, df=98). i.e., patients with thinner corneas were not more likely to have a thinner N-RRA.
- Increase in disc area was accompanied by an increase in C/D (Figure 3) – this increase was associated with a non-significant increase in N-RRA (t=0.99 p=0.32, df=98).
- Small discs which had a C/D greater than 0.5 tended to have small N-RRA (t=-8.21 p=0.000, df=93).

The Relation Between Structures

Pearson's Chi-square (ChiSq) is used to test whether data samples are different enough in some characteristic that we can generalize that the populations from which our samples are drawn are also different in the characteristic. Presuming that our young normal patient group's ONH structure can be extrapolated to represent the population from which it was sampled, we accepted a chi-square probability of .05 or less as justification for asserting that our young normal patients had ocular structure relations different from those expected by chance.

There were complete data on 532 young normal patients. We present Chi-square analysis for the right eye for differences from expected findings for the various parameters and their interactions (*see Table 3*). The C/D ratio and N-RRA were both different from expected findings at greater than the p(ChiSq)=0.05 level and the over-all data for a single parameter were different

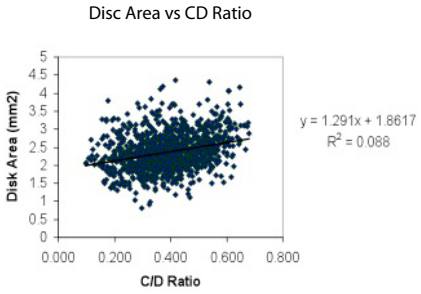

Figure 3: *Data presented are for 1404 eyes (702 patients – 621 with normal and 81 with high IOP [>21mmHg]). Increase in disc area was accompanied by a modest increase in C/D and N-RRA. Small nerves which had a large C/D tended to have small N-RRA (t=-8.21 p=0.000, df=93).*

from expected at p(ChiSq)=0.000 (ChiSq=26.419). For interaction of two parameters the C/D + C/D asymmetry, C/D + N-RRA, C/D asymmetry + N-RRA and Disc Area + N-RRA were all different from expected findings at greater than p(ChiSq)=0.028 and the over-all data for a two parameter interac tion were different from expected at p(ChiSq)=0.000 (ChiSq=83.877). For interaction of three parameters, ChiSq is not strictly appropriate and correction needs to be made due to the small numbers of expected findings. When analyzed with cor rection for continuity, the total ChiSq is very high (p(ChiSq)=0.000, ChiSq=81.540). With correction for continuity, the multiple interactions of CCT + C/D + Disc Area, CCT + C/D + N-RRA, CCT + C/D asymmetry + Disc Area, and C/D + C/D asymmetry + N-RRA were all different from expected findings at greater than p(ChiSq)=0.016.

TABLE 3A

SINGLE PARAMETER – 1SD

	Suspicious		Not-suspicious		
	Observed	Expected	Observed	Expected	ChiSq
CCT	93	84.40	439	447.60	
C/D	120	84.40	412	447.60	0.000
C/D Asymmetry	81	84.40	451	447.60	
Disc Area	98	84.40	434	447.60	
N-RRA	66	84.40	466	447.60	0.045
				Total C^2	0.000

SINGLE PARAMETER – 2SD

	Suspicious		Not-suspicious		
	Observed	Expected	Observed	Expected	ChiSq
CCT	10	12.10	522	519.90	
C/D	16	12.10	516	519.90	
C/D Asymmetry	20	12.10	512	519.90	0.023
Disc Area	19	12.10	513	519.90	
N-RRA	3	12.10	529	519.90	0.009
				Total X^2	0.001

TABLE 3B

TWO INTERACTIONS

	Suspicious		Not-suspicious		
	Observed	Expected	Observed	Expected	ChiSq
CCT + C/D	20	20.977	512	511.023	
CCT + C/D Asymmetry	9	14.160	523	517.840	
CCT + Disc Area	16	17.132	516	514.868	
CCT + N-RRA	11	11.538	521	520.462	
C/D + C/D Asymmetry	28	18.271	504	513.729	0.023
C/D + Disc Area	26	22.105	506	509.895	
C/D + N-RRA	45	14.887	487	517.113	0.000
C/D Asymmetry + Disc Area	21	14.921	511	517.079	
C/D Asymmetry + N-RRA	17	10.049	515	521.951	0.028
Disc Area + N-RRA	4	12.158	528	519.842	0.019
				Total X^2	0.000

TABLE 3C

THREE INTERACTIONS

	Suspicious		Not-suspicious		
	Observed	Expected	Observed	Expected	ChiSq
CCT + C/D + C/D Asymmetry	4	3.194	528	528.806	
CCT + C/D +Disc Area	11	3.864	521	528.136	0.001
CCT + C/D + N-RRA	9	2.602	523	529.398	0.000
CCT + C/D Asymmetry +Disc Area	7	2.608	525	529.392	0.013
CCT + C/D Asymmetry + N-RRA	2	1.757	530	530.243	
CCT + Disc Area + N-RRA	1	2.125	531	529.875	
C/D + C/D Asymmetry + Disc Area	7	3.366	525	528.634	
C/D + C/D Asymmetry + N-RRA	13	2.267	519	529.733	0.000
C/D + Disc Area + N-RRA	3	2.742	529	529.258	
C/D Asymmetry + Disc Area + N-RRA	2	1.851	530	530.149	
				Total X^2	0.000

TABLE 3D

FOUR OR MORE INTERACTIONS

	Suspicious		Not-suspicious	
	Observed	Expected	Observed	Expected
CCT + C/D + C/D Asymmetry + Disc Area	2	0.588	530	531.412
CCT + C/D + C/D Asymmetry + N-RRA	2	0.396	530	531.604
C/D + C/D Asymmetry + Disc Area + N-RRA	2	0.418	530	531.582
CCT + C/D + C/D Asymmetry + Disc Area + N-RRA	1	0.073	531	531.927

Between site measures

Between site measures were generally not significantly different. There were smaller over-all Disc Area in Canada (7087.28+/-1871.16 vs 7392.73+/-1714.24 pixels) and smaller over-all N-RRA in Canada (4413.98+/-1263.43 vs 4851.50+/-1379.51 pixels). These differences were significant at the 0.01 level when comparing Caucasian patients from Canada and the US.

Optos Measures

Conversion from pixels to disc area in mm²

We developed a conversion from Optos measures in pixels to disc area in mm². The result is shown in Figure 4. This conversion, which was determined by comparison of Optos and OCT performed on 82 eyes, is pixels multiplied by 0.0003.

Reliability

We investigated reliability of Optos measurements in three ways. First, we measured disc area with two scorings of one Optos measure by the same examiner on separate occasions on 20 patients. There was no significant difference, test-retest reliability (coefficient of correlation) was 0.91, and Reliability (Standard Error of Measurement) at the 95% confidence interval (CI) was 415 pixels (0.12mm²). Second, we measured C/D ratio with two scorings of one Optos measure by the same examiner on separate occasions on 20 patients and found no significant difference, a correlation of 0.79, and a 95% CI of 0.034. Third, we measured disc area with two different Optos images on separate occasions for 20 eyes and found a significant difference (t=-3.19, p=0.01), a correlation of 0.39, and a 95% CI of 171 pixels (0.05mm²). Based on our average of 7863.54 pixels/optic nerve, 171 pixels is about 2.2% (or in area, the average optic nerve would be 2.36mm² with a confidence of 0.05mm²).

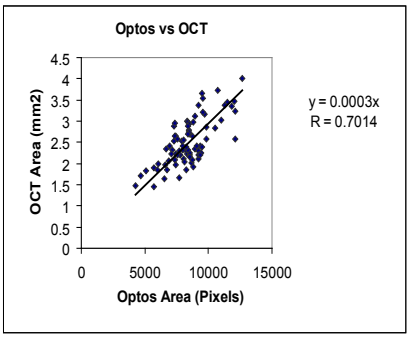

Figure 4: *Data are for 82 eyes (41 patients). Measurements were made first with Optos to determine disc area in pixels and then for the same patients with OCT to determine disc area in mm². The figure compares Optos values for disc area (in pixels) and OCT values (in mm²) for the same patients. The conversion factor from pixels to disc area (mm²) is pixels times 0.003. The data are modestly correlated (r = 0.70); we attribute the lack of higher correlation to "noise" between the two sets of data collected.*

Power Calculation

Using data from this study (sample size, C/D ratios and standard deviations for each group) the power level approaches 1 which indicates that these results have a greater level of power than 0.8 and level of statistical significance greater than 0.05.

Discussion

The clinical dilemma is that only a small proportion of patients ever develop glaucoma, and up to 50% of current patients with glaucoma do not know they have the disease. From our Research Objective:

- To provide data for young normal patients, gathered using screening devices available in a routine clinical setting, which delineate the normal range of specific physical ocular structures (CCT, C/D ratio, inter eye C/D ratio asymmetry, optic disc area, and N-RRA) as well as the interrelation between structure findings.

For young normal patients a statistically abnormal structure related to glaucoma (1SD from the mean) was a:

- central corneal thickness of 510.90µm (550.37 +/- 39.47) or less,
- C/D ratio of 0.50 (0.39 +/- 0.11) or more,
- Disc area of 9493.96 pixels (7863.54 +/- 1630.42); 2.85mm² or more,
- Between eye C/D ratio asymmetry of 0.08 (0.02 +/- 0.06) or more, and
- Neuro-retinal rim area of 3624.74 pixels (4785.88 +/- 1161.14); 1.09mm² or less.

The mean total Z-Score for our young normal population was 0.00 +/- 2.30 (range -7.32 to +9.24); 77.04% of young normal patients had a Z-score <2.30, 22.96% of patients were more than 1SD greater than the mean (Z-score >2.30), and 6.48% were more than 2SD greater than the mean. For the patients being treated for

glaucoma, using individual structure Z-Scores derived from the ocular structure mean and standard deviation of young normal patients, the mean total Z-Score was 3.25 (range -2.09 to +11.30). A Z-Score >2.30 was present in 65.52% of patients being treated for glaucoma.

There are similarities in specific physical ocular structures between a clinically significant number (22.96%) of healthy pre-presbyopic patients and patients being treated for glaucoma. These results provide an affirmative answer to our Specific Research Question:

- Are there clinically significant numbers of healthy pre-presbyopic patients and patients being treated for glaucoma who have similar specific physical ocular structure relationship?

In addition to the association (overlap) in IOP ranges between normal patients and those with glaucomatous visual field loss (*see Figure 1*), we found that there is also a significant overlap in the normal ranges of CCT, C/D ratio, C/D ratio asymmetry, disc area, and N-RRA between young normal patients and patients being treated for glaucoma (*see Figure 2*). Taken together, and using clinical, along with family risk factors, IOP values, and screening visual field (e.g., frequency doubling), these results can be used to refine decisions on which primary care patient to screen for glaucoma.

The physical ocular structures (CCT, C/D ratio, C/D ratio asymmetry, optic disc area and N-RRA) of subjects with abnormal findings (greater than one standard deviation from the mean) are related in Table 3. The C/D ratio and N-RRA were different than expected by chance as were interactions between C/D + C/D asymmetry, C/D + N-RRA, C/D asymmetry + N-RRA, and Disc Area + N-RRA. Further, the relation between multiple physical ocular structures CCT + C/D + Disc Area, CCT + C/D + N-RRA, CCT + C/D asymmetry + Disc Area, and C/D + C/D asymmetry + N-RRA were also different than expected by chance (*see Table 3*). The frequent appearance of CCT in the statistically significant multiple interactions of our young adults compares well with the OHTS data where a relation between thin CCT and glaucoma was found.[28]

Study Limitations

Study limitations include the testing approach, examination technique, lack of definition of race, and the patients on whom it was done. Recall that our testing approach is to determine the normal values (range, mean, and standard deviation) of glaucoma specific physical ocular structures and relating these for young normal and glaucoma patients. Either screening devices available in routine clinical care (e.g. NCT for IOP, Optos for C/D evaluation) or gold standard testing (e.g., Goldmann tonometry for IOP, Stereo optic nerve photos for C/D evaluation) may be used. Once the normative data have been determined it is irrelevant which clinical equipment was used; it is only required that decisions as to which structures are abnormal be made by applying equipment consistently between groups.

Our design is limited by the examination technique. We relied on ophthalmic examination and young age to maximize the probability that the young subjects did not manifest glaucomatous neuropathy. We performed threshold visual fields and nerve fiber analysis (GDx) on most young patients with abnormal ocular structure and none of them were identified with visual field or nerve fiber layer defects (and the vast majority also had normal IOP measures). As a result, we think it is unlikely that the normative ocular structure findings in our young patients were significantly influenced by the presence of patients with glaucoma.

Results comparing different ethnic groups depend on the definition of race used in the study. We used self-reported race in analysis (as have many other studies) and self-report of race is frequently unreliable. For example, in the Bureau of Census' Current Population Survey (March 1971 and March 1972) 34.2% of the same household reported different ethnic identities.[33] Because self-report is not always reliable it is possible that some persons were misclassified. Misclassification would weaken our ability to identify differences among ethnic groups. Further, our study was limited to persons living at just two separate sites (Houston, Texas and Oakville, Ontario) and may not generalize to persons of similar reported ethnicity living elsewhere.

Our study included young patients coming for an eye examination and was not population based. It is possible that persons who feel they require a vision examination, who

often have a significant refractive error, have different parameters of CCT, C/D ratio, inter eye C/D ratio asymmetry, optic disc area, and N-RRA than those who do not seek eye examinations. The aver age refractive error of the patients was -1.68 - 2.46 (range +7.25 to -11.50DS; 0.00 to -5.25DC). Only 0.91% were highly myopic (>-8.00) patients (who have been shown to be at greater risk for glaucoma and who tend to have large optic disc areas).[23] This, plus our finding that the average optic disc area was well within expected limits (see below), makes it likely that our results will generalize reasonably well to the persons with little or no refractive error who make up a large portion of the population.

Disc and N-RRA Area

Although digitized fundus photographs, confocal scanning laser ophthalmoscopy, scanning laser polarimetry and optical coherence tomography have all been used to evaluate optic disc topography[34], there is not one clearly identified "gold standard". To facilitate gathering of data, we elected to use Optos for our study. Optos is available in a large number of primary eyecare practices and its use allows this study to generalize to routine clinical vision care. Again, either screening devices or gold standard testing could be used to create a normative data base of glaucoma specific physical ocular structures; it is only required that decisions as to which structures are abnormal be made by applying equipment consistently between groups. The Optos has software (V^2 Vantage 2.3.0.70) that calculates C/D ratio and optic disc area in pixels. The basis for the topographic algorithm that permits C/D ratio calculation has not been published.

Conversion of Optos Measures (pixels) to mm^2

We developed a conversion to convert Optos measures in pixels to disc area in mm^2. This conversion, which was determined by performing Optos and OCT on 82 eyes, is pixels multiplied by 0.0003 (*see Figure 4*). Applying this factor to our over-all data for optic disc area and N-RRA gives

Average Optic Disc Area
(7863.57 × 0.0003) = 2.36mm^2
Optic Disc St Dev
(1630.42 × 0.0003) = 0.49mm^2
Average N-RRA
(4785.88 × 0.0003) = 1.44 mm^2
N-RRA St Dev
(1161.14 × 0.0003) = 0.35mm^2.

When the standard deviation is taken into account the average range for the optic disc area would be between 1.87mm^2 ([7863.57-1630.42] ×0.0003) and 2.85mm^2 ([7863.57+1630.42] ×0.0003). A thin N-RRA could be defined as one standard deviation below the mean; this would be 3624.74 pixels (4785.88 -1161.14) and would give a minimum expected N-RRA of 1.09mm^2 (3624.74 × 0.0003).

Published norms for the HRT II[34], which determines optic disc area and other neuro-retinal rim parameters, are a normal range of optic disc area between 1.69 and 2.82mm^2 and a minimum N-RRA of 1.20mm^2. These values correspond well to those we found (disc area = 1.87 to 2.85mm^2, minimum N-RRA = 1.09mm^2). Additionally, we found that our examiners use Optos to measure disc area with a 95% CI of 415 pixels (0.12mm^2), C/D ratio with a 95% CI of 0.034, and with repeatability of 171 pixels (0.05mm^2). Although the difference in repeatability is statistically significant, neither it nor the others are likely to be clinically significant. Taken together, these results suggest that the Optos (and, although not addressed by our data, perhaps other digitizing retinal cameras as well) can be used to accurately estimate C/D ratio, disc area, and neuro-retinal rim area.

Site Differences

For Caucasian patients, our Canadian patients had smaller optic disc areas (7087.99+/-1871.1 vs 7392.88+/-1714.24) and thinner over-all N-RRA (4413.98+/-1263.43 vs 4841.50+/-1379.51) than Texas patients. These differences were significant at the 0.01 level. It is likely that the difference stems from subtle differences in the drawing of the optic nerve parameters by the investigators. The dif ference would be about 0.09mm^2 ([7392.88 – 7087.28] × 0.0003), similar to our reliability findings, and is unlikely to have any clinical significance.

Racial differences in corneal thickness, C/D and optic disc area.

Racial differences in corneal thickness were found in the OHTS.[28] Since the OHTS subjects only included patients with ocular hypertension, it is reasonable to question whether these racial CCT differences would also be found in a clinical population with normal IOP

or whether the OHTS differences were somehow related to ocular hypertension. Our results demonstrate a difference in CCT for patients over a broad range of ages and over all self-designated races (*see Table 2*). In addition to racial differences in CCT in our young patients, there were racial differences in C/D ratio and optic nerve structure, as well as differences in their interrelations. Similar racial differences in C/D ratio and optic nerve structure have been reported in glaucoma patients.[25,27]

Clinical Application: Glaucoma Related Abnormal Structure Screening

We are suggesting that decisions regarding which primary eye care patient to screen for glaucoma may be refined through increased knowledge of and attention to the normal range and interrelation among the CCT, C/D ratio, inter eye C/D ratio asymmetry, optic disc area, and N-RRA. Determining the relation between structures lends itself to a proposed Glaucoma Related Abnormal Structure Screening (GRASS). From Figure 2, 22.96% of young normal patients and 65.52% of glaucoma patients have a Z-Score of 2.3 or greater.

A clinician could calculate the Z-score of each patient to accurately determine the deviation of ocular structures from the mean. However, rapid determination of Z-scores is not a clinically easy task. One method of rapidly estimating the Z-score is to define abnormal structure as 1SD from the mean and assign each abnormal structure (CCT, C/D ratio, inter eye C/D ratio asymmetry, optic disc area, and N-RRA) one point. This results in a 5 point score when all structures are abnormal (similar to that used for evaluation of many other ocular structures and functions).

From Table 4, patients with two or more abnormal structures (GRASS score of 2 or more) make up 18.72% of the young normal population and 74.55% of our glaucoma population (numbers that are similar to the Z-Score results in Figure 2). Further, the percentages of patients with multiple structural abnormalities (who receive a GRASS score of 3 to 5) correspond well to numbers found in prospective glaucoma incidence studies.[16,35-37] Indeed, the proportion of patients with abnormal ocular structure interrelation was as expected – higher for Black[30], intermediate for Hispanic[38], and lowest for Caucasian patients.[30] Taken together, these results suggest that simply scoring one point for each abnormal structure (CCT, C/D ratio, inter eye C/D ratio asymmetry, optic disc area, and N-RRA) will provide a useful clinical approximation of the abnormal structure ranking.

GRASS is an equipment-neutral procedure / approach. The mean and standard deviation of a structure is determined using a given piece of equipment (e.g, for C/D either Optos or the gold standard stereo photo could be used). The structure abnormality is then converted to a Z-score and this score is used in the GRASS calculation. In this manner, any given clinic can de-

TABLE 4

GLAUCOMA-RELATED ABNORMAL STRUCTURE SCREENING (PERCENT PER CATEGORY)

Grass Score	0	1	2	3	4	5
Black	38.06	38.85	14.44	6.82	1.57	0.26
Caucasian	53.08	35.78	10.26	0.59	0.29	0.00
Hispanic	56.29	27.67	11.64	3.77	0.63	0.00
Asian	43.24	33.78	14.86	8.11	0.00	0.00
Other (Indian/Pakistani)	46.20	27.17	21.74	4.89	0.00	0.00
All	49.82	32.79	12.97	4.46	0.36	0.09

Grass Score	0	1	2	3	4	5
Glaucoma	5.45	20.00	32.73	29.09	12.73	0.00

determine a GRASS score as long as they have confidently determined the mean and standard deviation of a physical ocular structure for their equipment. If they use Optos, our numbers can be used.

Glaucoma Related Abnormal Structure Screening (GRASS) Clinical Example

Consider the optic discs Figure 5a and 5b. In Figure 5a is an optic disc of a 26 year old Asian female with a C/D of 0.60 and in Figure 5b is the optic disc of a 15 year old Hispanic male with a C/D of 0.50. Based on C/D ratio alone a clinician would suspect that the patient in Figure 5a has a more abnormal structure. However, applying GRASS provides further information.

The patient in Figure 5a has a corneal thickness of 600µm, an optic disc area of 4.22mm^2 (14068 pixels), an inter-eye C/D ratio asymmetry of 0.01, and a neuro-retinal rim area of 1.69mm^2 (5627 pixels). Clearly, although she has a large C/D ratio and her optic disc area is very large, her inter-eye C/D ratio asymmetry and neuro-retinal rim area are both within the normal range. This gives her a Glaucoma Related Abnormal Structure Scale (GRASS) score of 2 – abnormal structures of large C/D and large optic disc area. Additionally, her measured IOP is 12 and, when corrected for corneal thickness, is even lower at 10.16 [12 – (0.50 × 3.69)].

The patient in Figure 5b has a corneal thickness of 495mm, an optic disc area of 1.95mm^2 (6512 pixels), an inter-eye C/D ratio asymmetry of 0.21, and a neuro-retinal rim area of 0.98mm^2 (3256 pixels). For this patient, although his optic disc area is small, he has a large C/D ratio, an abnormal inter-eye C/D ratio asymmetry, and his neuro-retinal rim area is well below normal. He has a high GRASS score of 4 since he has borderline C/D, thin cornea, inter-eye C/D asymmetry, and thin neuro-retinal rim. His IOP is 20 and, when corrected for corneal thickness, is above normal at 22.03 [20 + (0.55 × 3.69)].

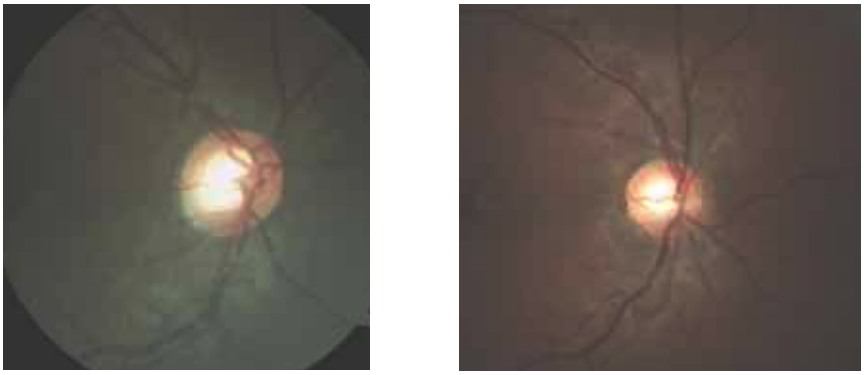

Figure 5a and 5b: *Figure 5a shows an optic nerve of a 26 year old Asian female with a C/D of 0.60 and in Figure 5b is the optic nerve of a 15 year old Hispanic male with a C/D of 0.50. The patient in Figure 5a has a GRASS score of 2 [optic nerve area of 2.82mm^2 (9399 pixels) and a neuro-retinal rim area of 1.21mm^2 (4041 pixels)]. The patient in Figure 5b has a GRASS score of 4 [corneal thickness of 495mm, C/D of 0.50, inter-eye C/D ratio asymmetry of 0.21, neuro-retinal rim area of 1.06mm^2 (3549 pixels)]. Although these patients should both be followed closely, the GRASS score suggests that the glaucoma related ocular structure in Figure 5b is of much more clinical concern than the one in Figure 5a.*

Although these patients could both be considered to have abnormal structure, the GRASS score suggests that the ocular structure of the patient in Figure 5b is much more abnormal than the one in Figure 5a. Based on analysis of these optic discs, the GRASS score has face validity – that is, it seems to make sense. It remains to be determined over time whether GRASS develops incremental validity in refining decisions on which primary eye care patient to screen for glaucoma (i.e., whether patients with greater scores actually show glaucomatous findings during glaucoma evaluation and subsequently go on to develop glaucoma in higher proportion to patients identified by other techniques).

Sensitivity and Specificity

Sensitivity is disease focused and describes the percentage of people with the disease that the test correctly identifies. A test with a sensitivity of 80% detects 80% of the abnormalities in the population studies (missing 20%). GRASS has a Sensitivity of 74.55% – the number of our glaucoma patients with a GRASS score of 2 or more.

Specificity is wellness or normal focused and describes the percentage of normal people the test

correctly identifies as normal. A test with 85% specificity correctly identifies 85% of healthy people as healthy (15% are false positives – thought to have the disease when they do not). GRASS has a Specificity of 81.28% – the number of normal patients with a GRASS score of 0 or 1.

The GRASS 74.55% Sensitivity and 81.28% Specificity rate is very high for a clinical screening test. For example, no single value of IOP is considered to provide an acceptable balance of sensitivity and specificity for screening[39]. For example, in the Baltimore Eye Survey[11], IOP ≥18 mm Hg had sensitivity and specificity of 65%; raising the cut-off to IOP ≥21 mm Hg improved specificity to 92% but lowered sensitivity to 44%. These results are due in part to fluctuations in IOP over time – only about 50% of patients with untreated glaucoma actually have IOP greater than 21 mm Hg on random measurement.[40] Although not tested by our data, presumably combining GRASS ocular structure screening with IOP could significantly raise the Predictive Value and provide a useful balance of sensitivity and specificity to determine which primary eye care patients to screen for glaucoma.

Conclusion

Data from this study provide new insight into the normal range and interrelation between CCT, C/D ratio, inter eye C/D ratio asymmetry, optic disc area, and N-RRA and positive answers to our General Research Questions:

1) Can decisions to determine which patients to screen for glaucoma be refined by determining the normal ranges of specific physical ocular structures?
2) And, can this normative data of specific physical ocular structures be applied to age range of patients that participated to find those with anatomy similar to glaucoma patients?

GRASS is an equipment-neutral tool for use by the general clinician to screen for relative ocular structure abnormality using the results of routine clinic tests. The GRASS score will help determine which primary eye care patient should be screened for glaucoma. In this view, the GRASS score would be considered along with other glaucomatogenic factors including age, IOP value, diurnal pressure fluctuation, optic nerve perfusion, visual field testing, etc. to determine the appropriate over-all level of concern.

GRASS is not intended to predict glaucoma development but rather to identify patients with multiple structural abnormalities, regardless of age or IOP level. Providing more information than a simple C/D ratio, evaluating and relating the ocular structures central corneal thickness, C/D ratio, inter-eye C/D ratio asymmetry, optic disc area, and N-RRA, in patients below age 40, will help refine decisions on which primary eye care patient to screen for glaucoma. This, in turn, will help identify which young patients should be more closely followed for possible future development of glaucoma.

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Footnotes

a. Patients being treated for glaucoma were those who, after thorough clinical evaluation, had been found to have continued and/or increasing nerve fiber layer loss (GDx or OCT) along with continued and or increasing visual field defects consistent with glaucoma (nasal step, bjerum scotoma, etc). These patients may or may not have had initial high IOP.

b. Except for corneal thickness, there were no statistically significant differences between male (555.01+40.55) and female (546.92+38.26) patients. Further, none of the between site measures were significantly different (except for two OPTOS measures). As a result, neither separate data for male and female patients nor between site measures are reported in Table 2.

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