Drug treatment


Short-term Effectiveness of Intravitreal Bevacizumab vs. Ranibizumab Injections for Patients with Polypoidal Choroidal Vasculopathy.

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PURPOSE: To compare the effectiveness of intravitreal injections of bevacizumab and ranibizumab in patients with treatment-naive polypoidal choroidal vasculopathy (PCV).

METHODS: Records from 106 consecutive patients who received intravitreal bevacizumab (n = 58, 1.25 mg) or ranibizumab (n = 52, 0.5 mg) for treatment of PCV were retrospectively reviewed. After three initial monthly loading injections, injection was performed as needed. The main outcome measures included best-corrected visual acuity (BCVA), foveal central thickness (FCT) as assessed by spectral domain optical coherence tomography, and the changes in polypoidal lesions based on an indocyanine green angiography.

RESULTS: The average number of injections was 3.31 ± 1.25 in the bevacizumab group and 3.44 ± 0.92 in the ranibizumab group. Mean logarithm of the minimum angle of resolution of BCVA from baseline to 6 months after injection improved by 0.17 in the bevacizumab group (p = 0.03) and by 0.19 in the ranibizumab group (p = 0.01). Average FCT decreased from 322 ± 62.48 µm to 274 ± 40.77 µm in the bevacizumab group (p = 0.02) and from 338 ± 50.79 µm to 286 ± 36.93 µm in the ranibizumab group (p = 0.02). Polyp regression rate was 20.7% (12 of 58 eyes) in the bevacizumab group and 21.2% (11 of 52 eyes) in the ranibizumab group. There was no statistically significant difference between groups in BCVA improvement achieved, FCT improvement achieved, and polyp regression rate between groups.

CONCLUSIONS: Intravitreal injections of bevacizumab and ranibizumab have similar effects in stabilizing visual acuity, macular edema, and regression of polypoidal complex in PCV eyes over the short term.

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Evaluation of Pain in Intravitreal Bevacizumab Injections.
Moisseiev E, Regenbogen M, Bartfeld Y, Barak A.

Department of Ophthalmology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.

Purpose: To evaluate the correlation between pain associated with intravitreal bevacizumab injection and the location of the injection.

Methods: The study included 218 eyes of 218 patients, who received an intravitreal bevacizumab injection at our institution. Pain was measured by the Visual Analog Scale (VAS). Additional parameters recorded included age, sex, indication for the injection, injection site by quadrant, number injections in the study eye, presence of diabetes mellitus, and lens status.

Results: Indications for injection included age-related macular degeneration (69.7%), diabetic macular edema (13.3%), neovascularization due to proliferative diabetic retinopathy (6.9%), and cystoid macular edema secondary to retinal vascular occlusions (10.1%). Pain scores on the VAS ranged from 0 to 84, with a mean of 17.4 ± 17.1. Pain did not correlate significantly with any of the recorded parameters, but a trend was found toward less pain associated with injection in the lower-left quadrant (p = 0.067).

Conclusions: This is the largest series studying the pain associated with intravitreal injections and provides a thorough description of the pain associated with this procedure. Since there is no anatomical difference between quadrants, we assume the demonstrated trend indicates that less pain is associated with the location in which it is most convenient for the ophthalmologist to perform the injection.

PMID: 22667326 [PubMed - as supplied by publisher]


Intravitreal anti-VEGF therapy blocks inflammatory cell infiltration and re-entry into the circulation in retinal angiogenesis.


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Purpose: Anti-VEGF-A antibody (Ab) (e.g. bevacizumab, ranibizumab) is widely used as a treatment against retinal angiogenesis and edema. The purpose of this study was to evaluate whether intravitreal anti-VEGF Ab injection modulates inflammatory cells in retinal angiogenesis.

Methods: To investigate whether intravitreal bevacizumab injection affects the number of inflammatory cells in proliferative diabetic retinopathy (PDR) membranes in patients, immunohistochemical staining with CD45 Ab (pan-leukocyte marker) was performed using the surgically obtained membranes in pars plana vitrectomy with or without pretreatment with bevacizumab. To check whether anti-VEGF-A Ab affects leukocytes going in and out of blood vessels during retinal angiogenesis, we performed our novel leukocyte transmigration assay and CD45 immunostaining in a mouse model of oxygen-induced retinopathy (OIR).

Results: Our new imaging approach revealed that intravitreal injection of anti-VEGF-A Ab blocks leukocyte infiltration as well as angiogenesis. The Ab injection inhibited leukocyte transmigration before affecting angiogenic area. CD45 staining showed no significant difference in leukocyte number in angiogenic retina or human PDR membranes between anti-VEGF-A Ab injected and control group. Furthermore, VEGF-A inhibition also affected leukocyte going out from retina.

Conclusions: Intravitreal injection of anti-VEGF-A Ab could inhibit leukocyte trafficking in retina, suggesting anti-VEGF-A therapy could serve to retinal inflammation.

PMID: 22661475 [PubMed - as supplied by publisher]
A new epidemiological aid in deciding whether to continue or stop a treatment.

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Purpose: To present a new epidemiological method relying on RCT data to assess whether a treatment was effective, aiding in the decision to continue or stop the treatment in clinical patients.

Methods: A cut-off point is calculated in the change of a continuous outcome for which a proportion of treated patients clearly achieved a change better than this cut-off point as a result of the treatment. This cut-off point can then be applied to individual patients during routine therapy. The method was applied to reports of the MARINA trial, which included patients with age-related macular degeneration treated with monthly intravitreal injections of ranibizumab, and to reports of trials involving patients with high intraocular pressure, macular edema and convergence insufficiency.

Results: The cut-off point in the change in visual acuity (numbers of letters), above which a proportion of patients clearly benefited due to ranibizumab treatment was 5.0 at 24 months follow-up. The proportions of treated patients who ended above this cut-off point due to the treatment was 60 per cent. The cut-off point varies with time of follow-up and by subgroup.

Conclusions: Contrary to common interpretation, no change, or a limited decline in the outcome (visual acuity), can still imply that the patients are better off with the treatment than with no treatment. Stopping the treatment above the cut-off point may not be appropriate since it was effective in at least a proportion of patients. This method applies to a broad range of scales and conditions.

PMID: 22661474 [PubMed - as supplied by publisher]
microdroplets, which is quite immediate and does not change significantly during the storage in terms of number and size.

CONCLUSION: Our results support the off-label use of repackaged bevacizumab by intravitreal administration, at least from a pharmaceutical point of view, with a validated stability of 3 months. This stability period is largely enough to practical situations and support current practices, such as in advance or batch preparations, which present major advantages in terms of GMP respect, workload optimization and financial savings.

PMID: 22655582 [PubMed - in process]


**Antiangiogenic therapy for ischemic retinopathies.**

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Abstract

Neovascularization is a common pathological process in various retinal vascular disorders including diabetic retinopathy (DR), age-related macular degeneration (AMD) and retinal vein occlusion (RVO). The development of neovascular vessels may lead to complications such as vitreous hemorrhage, fibrovascular tissue formation, and traction retinal detachments. Ultimately, irreversible vision loss may result. Various proangiogenic factors are involved in these complex processes. Different antiangiogenic drugs have been formulated in an attempt to treat these vascular disorders. One factor that plays a major role in the development of retinal neovascularization is vascular endothelial growth factor (VEGF). Anti-VEGF agents are currently FDA approved for the treatment of AMD and RVO. They are also extensively used as an off-label treatment for diabetic macular edema (DME), proliferative DR, and neovascular glaucoma. However, at this time, the long-term safety of chronic VEGF inhibition has not been extensively evaluated. A large and rapidly expanding body of research on angiogenesis is being conducted at multiple centers across the globe to determine the exact contributions and interactions among a variety of angiogenic factors in an effort to determine the therapeutic potential of antiangiogenic agent in the treatment of a variety of retinal diseases.

PMID: 22675660 [PubMed - in process]


**Serum concentrations of vascular endothelial growth factor in an infant treated with ranibizumab for retinopathy of prematurity.**


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PMID: 22672259 [PubMed - as supplied by publisher]
Comparison of different treatment intervals between bevacizumab injection and photodynamic therapy in combined therapy for age-related macular degeneration.

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PURPOSE: To compare the results of combination therapy with different intervals between intravitreal bevacizumab and photodynamic therapy (PDT) with verteporfin for age-related macular degeneration.

METHODS: Treatment-naïve eyes (n = 184) with 12 months' follow-up were included in this retrospective case series. Eyes were classified according to the interval between bevacizumab and PDT administration: group D1, 1-day interval (n = 116); group D7, 7-day interval (n = 68). The study was conducted at two hospitals, with group D1 evaluated in one hospital and group D7 evaluated in the other. The main outcome measure was comparison of the increases in best-corrected visual acuity (BCVA) of the two groups 3 and 12 months after the initial treatment by means of analysis of covariance (ANCOVA).

RESULTS: Group D1 gained 1.3 lines and group D7 gained 1.5 lines of BCVA at 3 months; group D1 gained 0.8 lines and group D7 gained 1.4 lines at 12 months. There was a significant difference between the groups in the increased BCVA levels at 3 months (P = 0.0450) and a trend toward significance at 12 months (P = 0.0516). ANCOVA analysis revealed that baseline BCVA, hemorrhagic pigment epithelial detachment, subretinal fluid, lesion size, and a 7-day treatment interval were significantly correlated with the increase in the BCVA at 3 months.

CONCLUSIONS: A 7-day treatment interval might offer slightly better visual acuity gain in the short term than a 1-day interval.
variety of ocular conditions, including age-related macular degeneration, diabetic eye disease, cystoid macular edema, and vascular occlusions. Patients undergoing an intravitreal injection procedure most commonly experience pain at the injection site, which has led physicians to explore the best means to decrease or to abolish pain sensation. Currently, no method of topical anesthesia prior to intravitreal injection administration has been proven to eliminate pain completely. Comparisons between different topical anesthetic agents have not yielded a consensus superior agent to be widely recommended for regular use. In order to minimize pain and reduce anxiety, addressing the patient's injection-related concerns is important.

PMID: 22657949 [PubMed - as supplied by publisher]

Other treatment & diagnosis


Topography of Geographic Atrophy in Age-related Macular Degeneration.


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Purpose: To determine the topographic distribution and progression of geographic atrophy (GA) in patients with age-related macular degeneration (AMD).

Methods: Fundus autofluorescence images (exc 488, em 500-700nm) from 413 eyes of 413 subjects (median age 77.0 years, Inter quartile range [IQR]72.0-82.0 years) of the Geographic Atrophy Progression (GAP)- study were retrospectively analyzed. Using a modified Early Treatment Diabetic Retinopathy Study grid to divide the posterior pole into nine different subfields plus periphery, the localization, size and progression of atrophic patches were determined. Subfields, zones (center, inner and outer) and slices (nasal, temporal, inferior, superior) were compared using the Friedman-test.

Results: The center and inner zones were involved in almost all eyes (>95%), while atrophy was less common in the outer zone subfields (76%). Inner zone atrophy size (median 4.00mm²) and progression rate (0.67mm²/year) were significantly greater than in the outer zone (0.60mm² and 0.42mm²/year)(p<0.001). There was a trend towards outer zone subfield and periphery involvement with increasing total size of atrophy. In addition, the superior outer subfield was significantly more affected by atrophy as compared to the other three outer subfields of the grid (p<0.001).

Conclusions: Distribution and progression of existing GA patches depend both on the eccentricity form the center and total GA size. Central macula areas appear most susceptible for the occurrence and expansion of GA. Refined analysis of distribution and directional spread is important to understand the natural history of the disease. This information will likely be helpful to design interventional GA clinical trials and associated anatomical outcome measures.

PMID: 22661483 [PubMed - as supplied by publisher]


The development & evaluation of two vision screening tools for correctable visual loss in older people.

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Objectives: In the UK, 20-50% of older people have undetected reduced vision and in most cases this results from correctable problems (refractive error and cataract). Many older people are not availing themselves of state-funded community optometric care. We assessed the efficacy of two vision screening instruments at detecting correctable visual problems and investigated the effect of optometric intervention on quality of life.

Methods: A computerised vision screener (CVS) was developed and refined after a preliminary study of 180 older people to include tests of: monocular presenting distance high contrast and low contrast visual acuities (VAs), binocular near acuities, and monocular visual fields. The modified CVS and a flip-chart vision screener (FVS) were evaluated on a second sample of 200 people aged 65+ (mean age 77 years). All participants in both studies were given an optometric eye examination, including high and low contrast VAs, refraction, binocular vision tests, tonometry, automated perimetry, and dilated fundoscopy including cataract grading and ARM grading. The target conditions were significant gain in monocular distance VA or binocular near VA with new refractive correction, significant cataract, or macular degeneration at risk of rapid progression. The Low Vision Quality of Life Questionnaire (LVQoL) was administered before and up to 3 months after testing.

Results: For the CVS, the best sensitivity (80.3%, 95% CI 72.4-86.4; specificity 66.7%, 95% CI 55.6-76.1) was obtained for a screener test combination of a fail on high contrast VA (>0.19 LogMAR) OR low contrast VA (>0.39 LogMAR) OR near VA (>N11.9). A screener test combination of high contrast VA OR near VA gave sensitivity of 79.5% (71.5-85.7) and specificity 67.9% (57-77.3). For the FVS, the best sensitivity was obtained for a test combination of a fail on high contrast VA OR low contrast VA OR near VA (sensitivity 82%, 95% CI 74.2-87.8; specificity 61.5%, 95% CI 50.4-71.6). A screener test combination of low contrast VA alone gave sensitivity of 75.4% (67.1-82.2) and specificity 76.9% (66.4-84.9). Significant improvements in LVQoL were found, with a significant correlation between gain in VA with new spectacles and improvement in LVQoL.

Conclusions: The vision screeners are effective tools for detecting those with reduced vision. Further work is required to determine their effectiveness as a tool for encouraging older people to engage in regular eyecare.

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En face enhanced depth imaging optical coherence tomography of fibrovascular pigment epithelium detachment.

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Department of Ophthalmology, University Paris Est Creteil, Centre Hospitalier Intercommunal de Creteil, Creteil, France.

Purpose: To analyze the internal structure of fibrovascular pigment epithelial detachment (FV-PED) due to age-related macular degeneration (AMD) using en face enhanced depth imaging (EDI) spectral-domain optical coherence tomography (SD-OCT).

Methods: We enrolled 38 consecutive patients presenting to our hospitals with FV-PED due to AMD. Retinal images were automatically obtained with the Spectralis SD-HRA+OCT; the typical inverted 97 sections at 30µm intervals, each comprised of 9 averaged B-scans, were acquired in less than 60 seconds. The resultant images of en face cross-sections of the choroid (C-scans) were compared with indocyanine green angiography (ICGA) images, currently the only technique available for directly viewing occult choroidal neovascularization (CNV).
Results: Thirty-eight eyes of 38 consecutive patients (27 females, mean age 76.7 ± 3 years) were studied. In all 38 eyes, ICGA allowed visualization of the CNV within the FV-PED. In 30 eyes, en face EDI-OCT revealed what appeared to be the hyperreflective course of presumed CNV which was located just beneath the detached retinal pigment epithelium; this was confirmed by comparative analysis of the extent of hyperreflective lesions on en face EDI-OCT images and that of the neovascular network on ICGA. An area of homogeneous hyporeflectivity, consistent with serous exudation, separated the CNV from the Bruch's membrane and the choroid. In the remaining 8 eyes, en face EDI-OCT revealed homogenous hyperreflectivity, consistent with fibrous tissue which partially hid the neovascular network.

Conclusions: Non-invasive en face EDI-OCT technique enables visualization and localization of the entire branching neovascular network of CNV within FV-PED without dye injection.

PMID: 22661465 [PubMed - as supplied by publisher]


Derivation, culture and retinal pigment epithelial differentiation of human embryonic stem cells using human fibroblast feeder cells.

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PURPOSE: Retinal pigment epithelium cells derived from human embryonic stem cells (ESCs) could be useful for restoring retinal function in age-related macular degeneration. However the use of non-human feeder cells to support the growth of ESCs for clinical applications raises the concern of possible contamination because of direct contact between animal and human cells.

METHODS: In this study, we produced human ESCs using human fibroblast feeder layers isolated from foreskin and abdominal tissues. Using this system, human ESCs differentiated into retinal pigment epithelium cells in differentiation medium.

RESULTS: Seven human ESC lines were established from 18 blastocysts. These human ESCs showed normal morphology, expressed all expected cell surface markers, had the ability to form embryoid bodies upon culture in vitro and teratomas after injection into SCID mice, and differentiated further into derivatives of all three germ layers. Under conditions of committed differentiation, these human ESCs could differentiate into retinal pigment epithelium cells after 2 months in culture.

CONCLUSIONS: The results of this study demonstrated that human foreskin/abdominal fibroblasts have the potential to support the derivation and long-term culture of human ESCs, which can then be used to generate retinal pigment epithelium cells with characteristic morphology and molecular markers. This technique avoids the concerns of contamination from animal feeder layers during human ESC derivation, culture and differentiation, and will thus facilitate the development of retinal pigment epithelium cell transplantation therapy.

PMID: 22661130 [PubMed - as supplied by publisher]


Embryonic stem-cell-derived retinal pigment epithelial cells for macular degeneration.

Falsini B, Bisti S.


PMID: 22656882 [PubMed - in process]

Embryonic stem-cell-derived retinal pigment epithelial cells for macular degeneration.

Huang J, McAlinden C, Wang Q, Jin ZB, Pesudovs K.


PMID: 22656881 [PubMed - in process]

Genetics


Modelling the genetic risk in age-related macular degeneration.

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Abstract

Late-stage age-related macular degeneration (AMD) is a common sight-threatening disease of the central retina affecting approximately 1 in 30 Caucasians. Besides age and smoking, genetic variants from several gene loci have reproducibly been associated with this condition and likely explain a large proportion of disease. Here, we developed a genetic risk score (GRS) for AMD based on 13 risk variants from eight gene loci. The model exhibited good discriminative accuracy, area-under-curve (AUC) of the receiver-operating characteristic of 0.820, which was confirmed in a cross-validation approach. Noteworthy, younger AMD patients aged below 75 had a significantly higher mean GRS (1.87, 95% CI: 1.69-2.05) than patients aged 75 and above (1.45, 95% CI: 1.36-1.54). Based on five equally sized GRS intervals, we present a risk classification with a relative AMD risk of 64.0 (95% CI: 14.11-1131.96) for individuals in the highest category (GRS 3.44-5.18, 0.5% of the general population) compared to subjects with the most common genetic background (GRS -0.05-1.70, 40.2% of general population). The highest GRS category identifies AMD patients with a sensitivity of 7.9% and a specificity of 99.9% when compared to the four lower categories. Modeling a general population around 85 years of age, 87.4% of individuals in the highest GRS category would be expected to develop AMD by that age. In contrast, only 2.2% of individuals in the two lowest GRS categories which represent almost 50% of the general population are expected to manifest AMD. Our findings underscore the large proportion of AMD cases explained by genetics particularly for younger AMD patients. The five-category risk classification could be useful for therapeutic stratification or for diagnostic testing purposes once preventive treatment is available.

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Purpose: To evaluate the pathogenicity of the G1961E mutation in the ABCA4 gene and to present the range of retinal phenotypes associated with this mutation in homozygosity in a patient cohort with ABCA4-
associated phenotypes.

Methods: Patients were enrolled from the ABCA4 disease database at Columbia University or by inquiry from collaborating physicians. Only patients homozygous for the G1961E mutation were enrolled. The entire ABCA4 gene open reading frame, including all exons and flanking intronic sequences, was sequenced in all patients. Phenotype data were obtained from clinical history and examination, fundus photography, infrared imaging, fundus autofluorescence, fluorescein angiography and spectral domain-optical coherence tomography. Additional functional data were obtained using the full-field electroretinogram, and static or kinetic perimetry.

Results: Twelve patients homozygous for the G1961E mutation were evaluated. All patients had evidence of retinal pathology consistent with the range of phenotypes observed in ABCA4 disease. The latest age of onset was recorded at 64 years, in a patient initially diagnosed with age-related macular degeneration (AMD). Six patients had severe structural (with/without functional) fundus changes detected, and in 5 of these cases additional, heterozygous or homozygous, mutations were detected in the ABCA4 gene.

Conclusion: Homozygous G1961E mutation in ABCA4 results in a range of retinal pathology. The phenotype is usually at the milder end of the disease spectrum, with severe phenotypes linked to the presence of additional ABCA4 mutations. This report also highlights that milder, late-onset Stargardt disease may be confused with AMD.

PMID: 22661473 [PubMed - as supplied by publisher]


Genetic Factors for Choroidal Neovascularization Associated with High Myopia.


Department of Ophthalmology, University Paris Est Creteil, Creteil, France.

PURPOSE: Non-syndromic high myopia defined by a refractive error greater than - 6 diopters (D), is associated with an increased risk of macular choroidal neovascularization (CNV), a vision-threatening complication. The aim of this study was to investigate whether genetic factors associated with age-related macular degeneration (AMD) are related to myopic CNV.

METHODS: We conducted a case-control study including 71 cases with myopic CNV and 196 myopic controls without CNV from Creteil (France), Toulouse (France) and Boston (MA, USA). Single nucleotide polymorphisms (SNPs) from 15 genes reported to be related to AMD were selected for this study.

RESULTS: In univariate analysis, the rs10033900 SNP located in CFI was associated with myopic CNV (P = 0.0011), and a SNP in APOE was also related. After adjustment for age, gender, degree of myopia, SNPs in 3 genes were associated including CFI (odds ratio (OR) 2.1, 95% confidence interval (CI) 1.3-3.37, P = 0.0023), COL8A1 (OR 1.88, P=.0076), and CFH (OR 1.65, P= 0.04) . After correction for multiple testing, only CFI remained significantly related to high myopic CNV (P=0.045).

CONCLUSIONS: The rs10033900 SNP located in the CFI gene, which is in the inflammatory pathway, is a plausible biological marker associated with CNV outgrowth among high myopic patients. Results generate hypotheses about potential loci related to CNV in high myopia and larger studies are needed to expand upon these findings.

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Macular degeneration genetics.

Bradley DT, Meng W, Hughes AE.
Belfast, United Kingdom.
PMID: 22656900 [PubMed - in process]

Diet

Effect of (R)-α-Lipoic Acid Supplementation on Serum Lipids and Antioxidative Ability in Patients with Age-Related Macular Degeneration.

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School of Public Health, China Medical University, Shenyang, China.
Background/Aims: Supplementation with antioxidants is of special interest in preventing or delaying the development and progression of age-related macular degeneration (AMD). This investigation aimed to assess the effect of α-lipoic acid (LA) on serum lipids, serum malondialdehyde (MDA) and superoxide dismutase (SOD) in patients with AMD.

Methods: A total of 62 patients (50-75 years old) with early and intermediate dry form of AMD were randomly assigned to two groups, i.e. LA administration (n = 32) and placebo (n = 30). The levels of serum lipids and MDA and SOD activity were measured before and after LA and placebo intervention.

Results: Compared with the parameters at baseline, serum total cholesterol (CHO), triglyceride and high- and low-density lipoprotein CHO (HDL and LDL) levels were not significantly different after LA and placebo intervention. There was a slight but statistically nonsignificant decrease in serum MDA levels and a statistically significant increase in serum SOD activity after LA intervention. There were no statistically significant differences in serum MDA levels or SOD activity after placebo intervention.

Conclusion: The apparent increase in SOD activity caused by LA supplementation indicates that LA may have a possible preventive effect in the development of AMD through an antioxidant mechanism.

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Discovery of human zinc deficiency: 50 years later.

Prasad AS.
Wayne State University School of Medicine, Department of Oncology and Barbara Ann Karmanos Cancer Center, Detroit, MI, USA.

Abstract

Essentiality of zinc for humans and its deficiency was recognized in 1963. During the past 50 years, it has become apparent that deficiency of zinc in humans is prevalent. Nutritional deficiency of zinc may affect nearly 2 billion subjects in the developing world. Consumption of cereal proteins high in phytate decreases the availability of zinc for absorption. Conditioned deficiency of zinc is also very common.


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Essentiality of zinc for humans and its deficiency was recognized in 1963. During the past 50 years, it has become apparent that deficiency of zinc in humans is prevalent. Nutritional deficiency of zinc may affect nearly 2 billion subjects in the developing world. Consumption of cereal proteins high in phytate decreases the availability of zinc for absorption. Conditioned deficiency of zinc is also very common.

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retardation, hypogonadism in males, rough skin, impaired immunity, neuro-sensory disorder and cognitive impairment are some of the clinical manifestations of zinc deficiency. Zinc is involved in many biochemical functions. Over 300 enzymes require zinc for their activation and nearly 2000 transcription factors require zinc for gene expression. Zinc is essential for cell mediated immunity. Zinc is also an effective antioxidant and anti-inflammatory agent. In therapeutic dosages, zinc has been used for the treatment of acute diarrhea in infants and children, common cold, Wilson's disease, sickle cell disease and for prevention of blindness in patients with age related macular degeneration.

PMID: 22664333 [PubMed - as supplied by publisher]