Paris
Ophthalmology Prevention

Ophthalmological Prevention

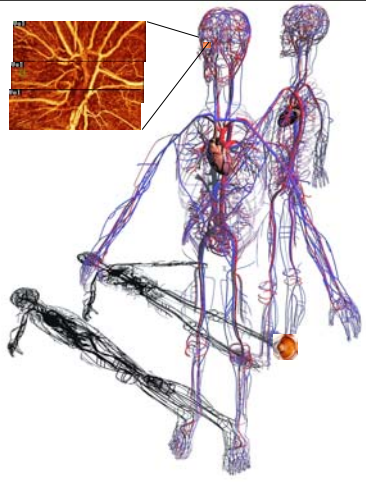
Telemedical System Offering Ophthalmological Preventive Medicine for Preventive Medicine Provider

Tele-OPM



Prof. Dr. Georg Michelson [1,2]

1) Department of Ophthalmology, University of Erlangen-Nürnberg
2) Private Tele-Ophthalmological Institute, Erlangen
michelson@t-online.de



„The Eye, Window to Brain and Heart“

michelson@t-online.de

Directory of Lessons

1. Background & Purpose
2. Anatomy & Physiology of Optical Pathway
3. Important Diseases in Ophthalmological Preventive Medicine
   - Retinal Microangiopathy
     - Arterial Hypertension
     - Diabetes
   - AMD
   - Glaucoma
4. Telemedical System Offering Ophthalmological Preventive Medicine: ***“Tele-OPM“***
5. Summary

Directory of Lessons

1. **Background & Purpose**
2. Anatomy & Physiology of Optical Pathway
3. Important Diseases in Ophthalmological Preventive Medicine
   - Retinal Microangiopathy
     - Arterial Hypertension
     - Diabetes
   - AMD
   - Glaucoma
4. Telemedical System Offering Ophthalmological Preventive Medicine: *"Tele-OPM"*
5. Summary

Lesson 1

- **Background & Purpose for Ophthalmological Preventive Medicine**

Background & Purpose #1:
Interdisciplinary prevention of cardio-vascular diseases extends years without activity loss (=healthy life span)

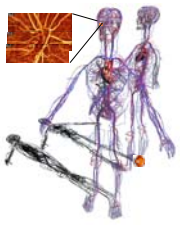
Background & Purpose #2:
The Eye Mirrors Vascular and Neurodegenerative Diseases

Retinal microangiopathy correlates with systemic diseases

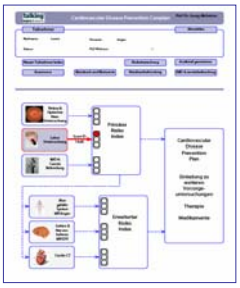
- **Arterial hypertension**
- **Diabetes**
- **Stroke**
- **Heart failure**

michelson@t-online.de

Background & Purpose #3:
Consequence→Interdisciplinary Prevention Network Including Retinal Vessel & Optic Nerve Head Evaluation

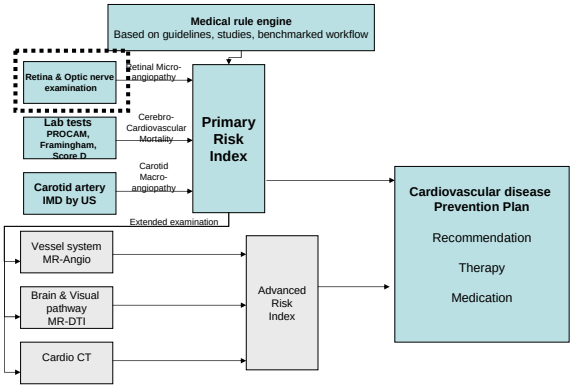


„The Eye, Window to Brain and Heart“



michelson@t-online.de

Background & Purpose #4:
Proposed Methodology for Interdisciplinary Prevention

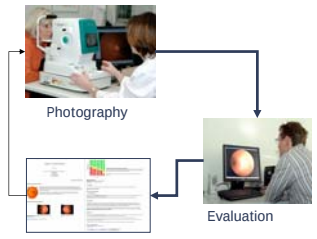


Purpose #1:

Aim: Telemedical System Offering Ophthalmological Expertise for Provider of Preventive Medicine

„Tele-OPM“ aims to offer

- *Tele-ophthalmological expertise for preventive medicine provider*



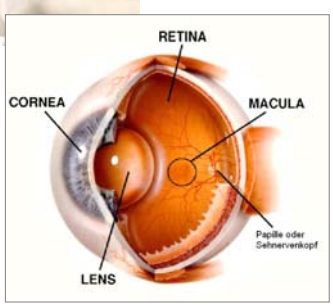
- **Photography in location A**
- **Evaluation in location B**

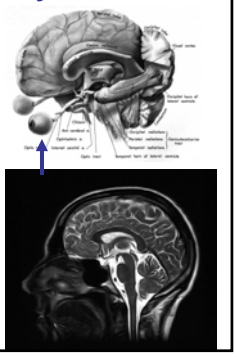
Directory of Lessons

Lesson 2

- **Anatomy & Physiology of Optical Pathway**

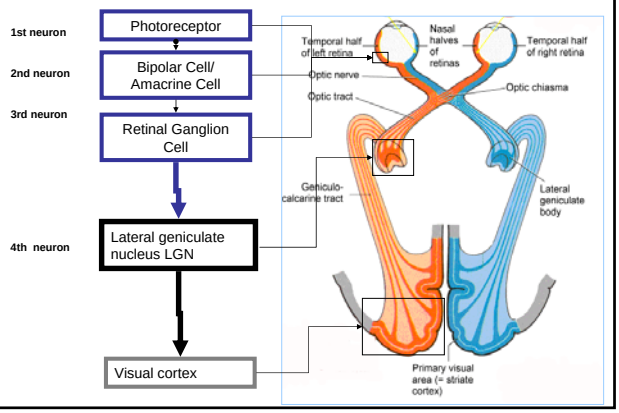
Eye and Optical Pathway





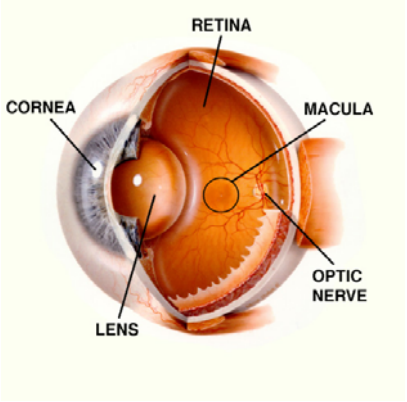
Anatomy 1:

The visual pathway is transsynaptic

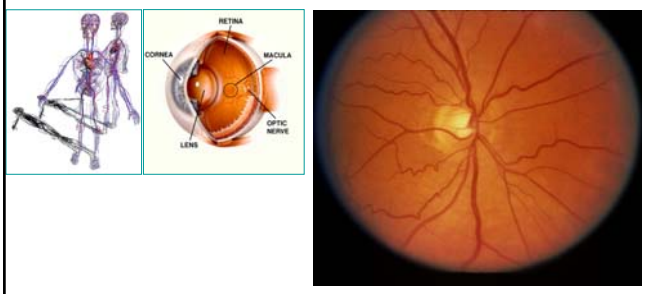


Anatomy 2:

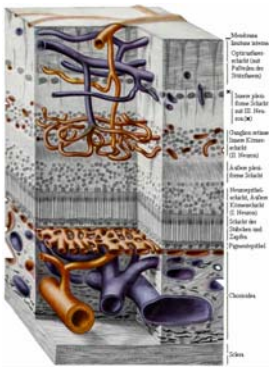
The eyeball is part of the visual pathway



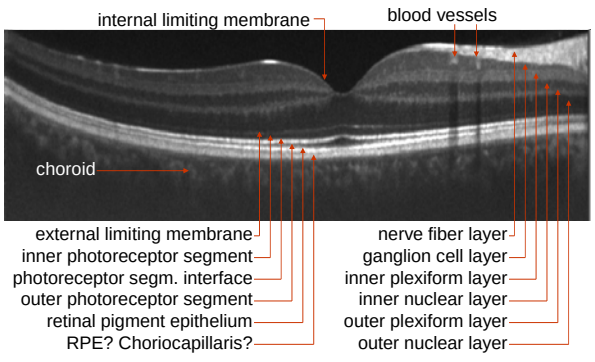
Anatomy 3:
Retina and optic nerve head



Anatomy 4:
Microstructure of the retina



Anatomy 5:
Microstructure of the macula by Optical Coherence Tomography OCT



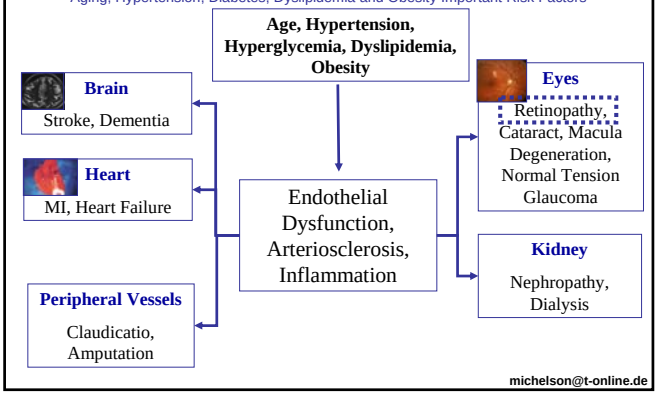
Directory of Lessons

Lesson 3

- **Important Diseases in Ophthalmological Preventive Medicine**
  - **Retinal Microangiopathy in Arterial Hypertension**

Hypertensive Retinopathy
Pathogenesis

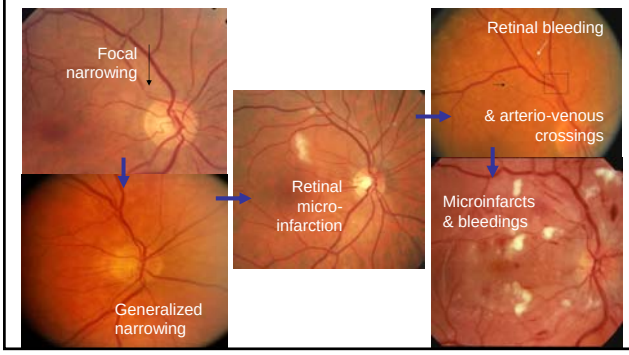
The Eye Mirrors Vascular and Neurodegenerative Diseases:
Aging, Hypertension, Diabetes, Dyslipidemia and Obesity Important Risk Factors

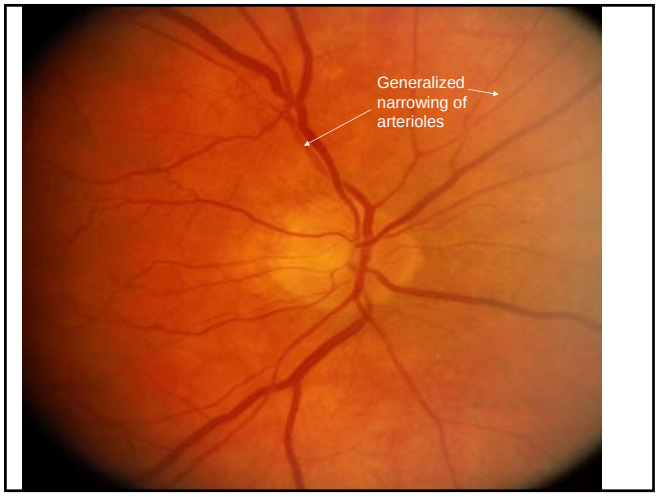


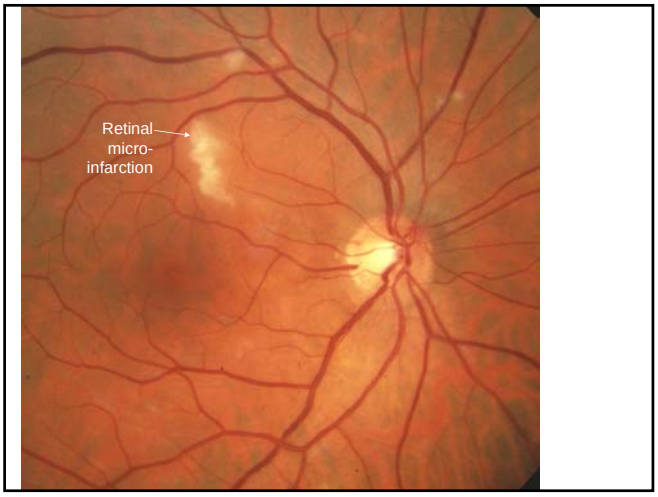
michelson@t-online.de

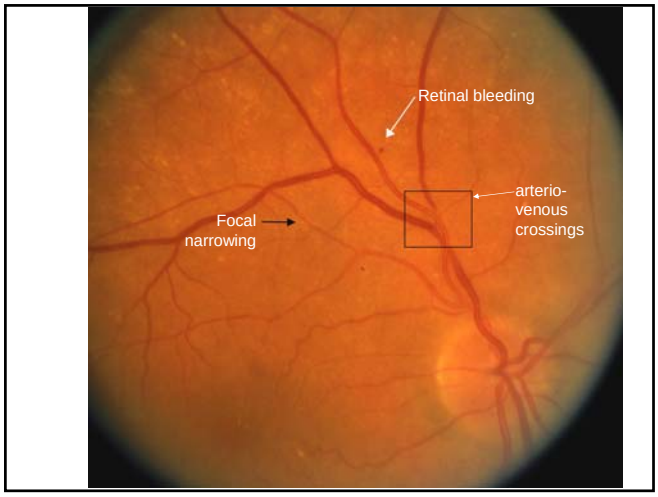
Hypertensive Retinopathy
Clinical Signs

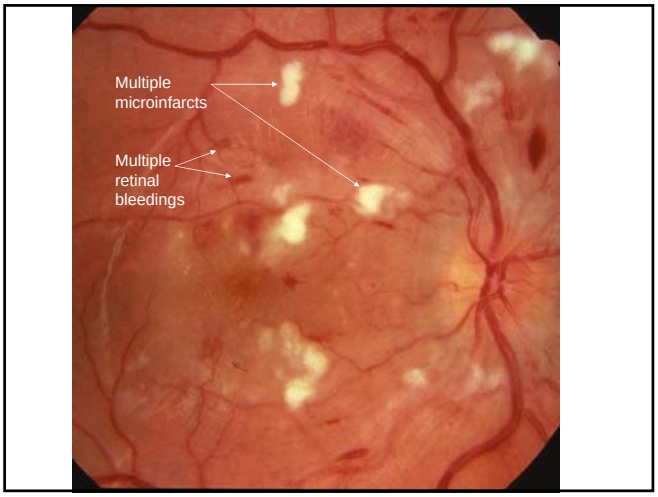
Aging, Hypertension, Diabetes, Dyslipidemia and Obesity → retinal microangiopathy




Generalized
narrowing of
arterioles


Retinal
micro-
infarction


Retinal bleeding
arterio-
venous
crossings
Focal
narrowing


Multiple
microinfarcts
Multiple
retinal
bleedings

Hypertensive Retinopathy
Risk Factors

- There is evidence, that **microangiopathic abnormalities of the retina** correlate with cerebro-cardiovascular risik factors
  - Metabolic syndrom[1]
  - Cardiovascular diseases[2]
  - Age & arterial hypertension[3]
  - Stroke[4,5]
  - Myocardial infarction[6]

1) Tien Yin Wong et al., Associations between the Metabolic Syndrome and Retinal Microvascular Signs: The Atherosclerosis Risk in Communities Study. IOVS 2004;45:2949-2954
2) Kamran Ikram et al., Are Retinal Arteriolar or Venular Diameters Associated with Markers for Cardiovascular Disorders? The Rotterdam Study. IOVS 2004;45:2129-2134
3) Harry Leung et al., Relationships between Age, Blood Pressure, and Retinal Vessel Diameters in an Older Population. IOVS 2003;44:2900-2904
4) Tien Yin Wong et al., Retinal microvascular abnormalities and incident stroke: the Atherosclerosis Risk in Communities Study, Lancet, 1134-1140, 2001
5) Kobayashi S, Okada K, Koide H, et al: Subcortical silent brain infarction as a risk factor for clinical stroke.Stroke 28:1932–9, 1997
6) Wong TY, Klein R, Nieto FJ, et al. Retinal microvascular abnormalities and ten-year cardiovascular mortality: a population-based casecontrol study. Ophthalmology 2003; 110: 933–40.

michelson@t-online.de

Hypertensive Retinopathy
Risk Factors

Retinal microangiopathy correlates with systemic diseases

- **Arterial hypertension**
- **Stroke**
- **Heart failure**
- **Diabetes**

michelson@t-online.de

Stroke risk and retinal microangiopathy

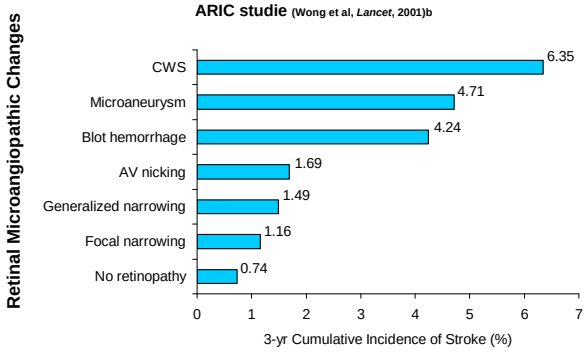
- **Highest evidence for association between retinal microangiopathy and stroke**
- retinal and cerebral circulation anatomically, physiologically and embryologically similar
  - Autopsy study in patients with stroke showed high correlation between retinal and cerebral vessel alterations
  - retinal blood flow decreased in patients with lacunar brain infarcts
- **4 great population-based studies demonstrated association between retinal microangiopathy and stroke**
- **The Atherosclerosis Risk in Communities study (ARIC)**:
  - 2-4-times increased stroke risk
  - Reduced cognitive capacity in standardized neuropsychological tests
  - Increased number of White-Matter Lesions
  - Cerebral atrophy (MRI)
  - 18-times increased stroke risk when simultaneous retinal microangiopathy and cerebral White-Matter Lesions
- **Cardiovascular Health Study**
  - 2-times increased stroke risk
- **Population-based studies in Wisconsin 45, and Japan 46:**
  - 2-3 times increased stroke risk independent of regular car**dio vascular risk factors**

michelson@t-online.de

Retinal Microangiopathy Predicts Vascular Diseases

3-years Risk for Stroke

ARIC studie (Wong et al, *Lancet*, 2001)b



michelson@t-online.de

Risk of ischemic heart failure and retinal microangiopathy

- **National Health Examination Survey**, when arteriolar narrowing
- **2 -6-increased r**isk for ischemic coronary heart disease (independent of hypertension, Diabetes, Cholesterol) 47

- **Study with 560** males with hypertension and hyperlipidemia
- When arteriolar narrowing then **2,9-times increased risk for** ischemic coronary heart disease 48

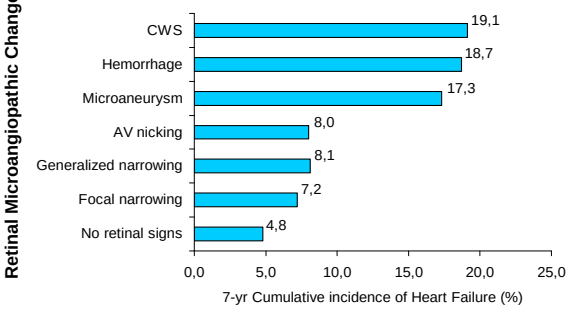
- **The Atherosclerosis Risk in Communities study**
- when arteriolar narrowing then **2,2-times increased risk for** ischemic coronary heart disease in females 49

michelson@t-online.de

Retinal Microangiopathy Predicts Vascular Diseases

7-years Risk for Heart Failure

ARIC study (Wong et al, *JAMA* 2005)

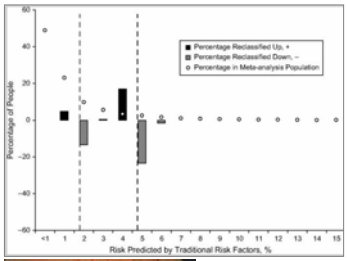


michelson@t-online.de

Hypertensive Retinopathy

Retina Check Improves Traditional Risk Scores

Inclusion of retinal vessel caliber in prediction models containing traditional stroke risk factors reassigned 10.1% of people at intermediate risk into different, mostly lower, risk categories

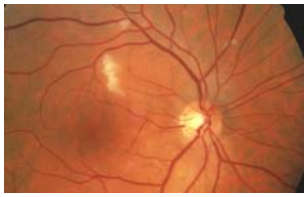


Am J Epidemiol. 2009 Dec 1;170(11):1323-32.
Prediction of incident stroke events based on retinal vessel caliber: a systematic review and individual-participant meta-analysis.
McGeechan K, Liew G, Macaskill P, Irwig L, Klein R, Klein BE, Wang JJ, Mitchell P, Vingerling JR, de Jong PT, Witteman JC, Breteler MM, Shaw J, Zimmet P, Wong TY.

michelson@t-online.de

Hypertensive Retinopathy

Diagnostics in Preventive Medicine

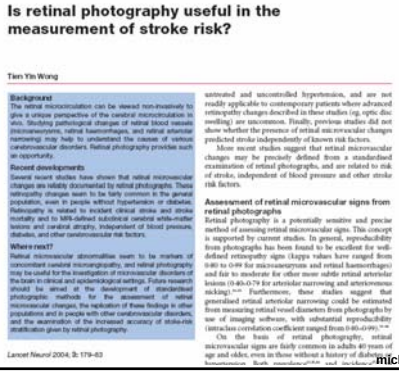


Colour Fundus Photography Allows Retinal Vessel Evaluation

michelson@t-online.de

Retinal Photography to Predict Cardiovascular Disease?

(Wong TY. *Lancet Neurology*, 2004)



Is retinal photography useful in the measurement of stroke risk?

Tien Yin Wong

Background

The retinal microcirculation can be viewed non-invasively to give a unique perspective of the cerebral microcirculation in vivo. Studying pathological changes of retinal blood vessels (microaneurysms, retinal haemorrhages, and retinal arteriolar narrowing) may help to understand the causes of various cerebrovascular disorders. Retinal photography provides such an opportunity.

Recent developments

Several recent studies have shown that retinal microvascular changes are reliably documented by retinal photographs. These retinopathy changes seem to be fairly common in the general population, even in people without hypertension or diabetes. Retinopathy is related to incident clinical stroke and stroke mortality and to MRI-defined subclinical cerebral white-matter lesions and cerebral atrophy, independent of blood pressure, diabetes, and other cerebrovascular risk factors.

Where next?

Retinal microvascular abnormalities seem to be markers of concomitant cerebral microangiopathy, and retinal photography may be useful for the investigation of microvascular disorders of the brain in clinical and epidemiological settings. Future research should be aimed at the development of standardised photographic methods for the assessment of retinal microvascular changes, the replication of these findings in other populations and in people with other cerebrovascular disorders, and the examination of the increased accuracy of stroke-risk stratification given by retinal photography.

Lancet Neurol 2004; 3: 179–83

untreated and uncontrolled hypertension, and are not readily applicable to contemporary patients where advanced retinopathy changes described in these studies (eg, optic disc swelling) are uncommon. Finally, previous studies did not show whether the presence of retinal microvascular changes predicted stroke independently of known risk factors.

More recent studies suggest that retinal microvascular changes may be precisely defined from a standardised examination of retinal photographs, and are related to risk of stroke, independent of blood pressure and other stroke risk factors.

Assessment of retinal microvascular signs from retinal photographs

Retinal photography is a potentially sensitive and precise method of assessing retinal microvascular signs. This concept is supported by current studies. In general, reproducibility from photographs has been found to be excellent for well-defined retinopathy signs (kappa values have ranged from 0·80 to 0·99 for microaneurysms and retinal haemorrhages) and fair to moderate for other more subtle retinal arteriolar lesions (0·40–0·79 for arteriolar narrowing and arteriovenous nicking).[5,6] Furthermore, these studies suggest that generalised retinal arteriolar narrowing could be estimated from measuring retinal vessel diameters from photographs by use of imaging software, with substantial reproducibility (intraclass correlation coefficient ranged from 0·85–0·99).[7,8]

On the basis of retinal photography, retinal microvascular signs are fairly common in adults 40 years of age and older, even in those without a history of diabetes or hypertension. Both [illegible] and [illegible]

michelson@t-online.de

Directory of Lessons

1. Background & Purpose
2. Anatomy & Physiology of Optical Pathway
3. **Important Diseases in Ophthalmological Preventive Medicine**
   - **Retinal Microangiopathy**
     - Arterial Hypertension
     - **Diabetes**
   - AMD
   - Glaucoma
4. Telemedical System Offering Ophthalmological Preventive Medicine:“Tele-OPM“
5. Summary

Lesson 4

- **Important Diseases in Ophthalmological Preventive Medicine**
  - **Diabetes or suspicious diabetes**

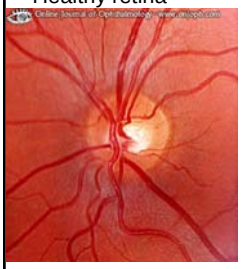
Diabetic Retinopathy

Clinical Signs

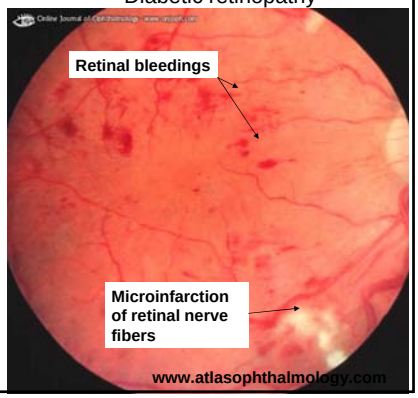
1. Microaneurysm
2. Retinal bleedings
3. Microinfarctions (Cotton-Wool-spots),
4. Hard exsudates
5. Venous beadings
6. Proliferative retinopathy

Diabetic Retinopathy
Clinical Signs #1

Healthy retina

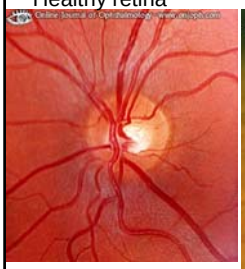


Diabetic retinopathy

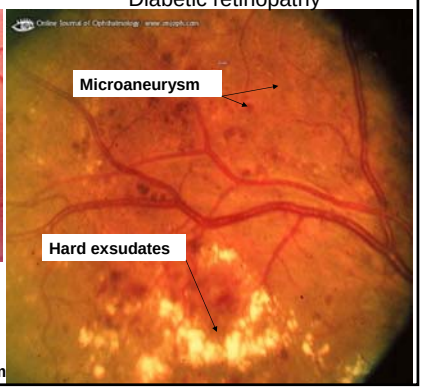


Diabetic Retinopathy
Clinical Signs #2

Healthy retina

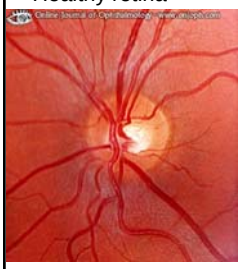


Diabetic retinopathy

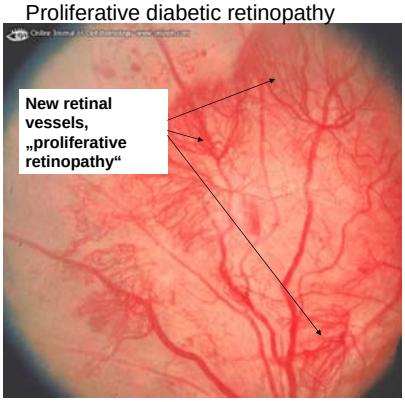


Diabetic Retinopathy
Clinical Signs #3

Healthy retina



Proliferative diabetic retinopathy



Diabetes
Diabetic Retinopathy in the World

2012: ca. 110 Mio patients with Diabetes

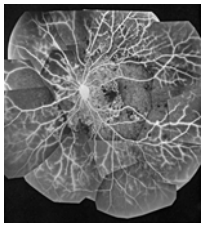
2030: ca. 290 Mio patients with Diabetes

25%- 70% of diabetes patients show diabetic retinopathy

Diabetic Retinopathy in %

after 10 years	35-50%
after 20 years	65-85%
after 30 years	75-90%

Consequence: >50.000 patients per year become blind by Diabetes



Diabetes
Economic Considerations

- **1992, 3.5% diabetics in USA, 15% of health budget for diabetes**
  - Rubin RJ, Altman WM, Mendelson DN: Health care expenditures for people with diabetes mellitus. J Clin Endocrinol Metab 78:809, 1994
- **2002, 7% diabetics in USA**
- **Screening of retina and early treatment cost-effectiv**
  - Javitt JC, Aiello LP, Chang YP: Preventive eye care in people with diabetes is cost saving to the federal government: Implications for health care reform. Diabetes Care 17:909, 1994

Diabetes
Prevalence of Diabetic Retinopathy

Type II diabetes

- **1-3** years after diagnosis:
  - **23%** of diabetics have retinopathy,
  - **2% proliferative r**etinopathy
- **20 years after** diagnosis:
  - **60%** of diabetics have retinopathy,
  - **5% proliferative** retinopathy

Diabetes
Risk of blindness in % of diabetic patients as a function of number of retinal signs of DR

When 1 out 4 signs: **6.7%**
When 2 out 4 signs: **8.5%**
When 3 out 4 signs: **26.7%**
When 4 out 4 signs: **36.9%**

Diabetic Retinopathy Study Research Group: Four risk factors for severe visual loss in diabetic retinopathy. Arch Ophthalmol 97:654, 1979

Retinal Signs of Diabetic Retinopathy (DR)

- Retinal bleedings
- Microinfarctions (Cotton-Wool-spots),
- Hard exsudates
- Venous beadings

Diabetes
Preventive Therapy
Early diagnosis & early Laser treatment of retina reduces the risk of blindness

- Laser treatment within 28 months

→ only in 6,4% proliferative diabetic retinopathy

- **No** Laser treatment within 28 months

→in **16%** proliferative diabetic retinopathy

- Diabetic Retinopathy Study Research Group: Preliminary report on effect of photocoagulation therapy. Am J Ophthalmol 81:383, 1976

Diabetes

Preventive Diagnostics

Need of early detection!

- Preventive medicine in suspicious diabetics
- All of them need a retinal evaluation
- one evaluation of the retina per year

Diabetes

Diagnostics in Preventive Medicine

Fundus photography

Colour Fundus Photography Allows Retinal Vessel Evaluation

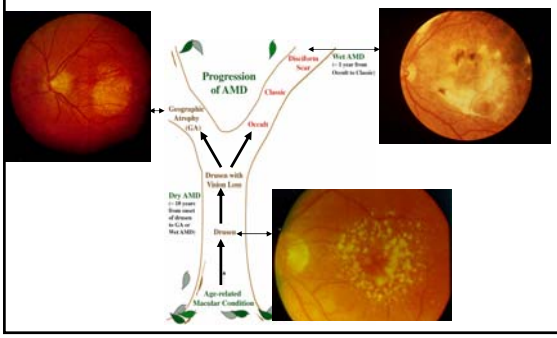
Directory of Lessons

Lesson 5

- **Important Diseases in Ophthalmological Preventive Medicine**
  - **Age-related Macula Degeneration AMD**

Age-related Macula Degeneration AMD
Pathogenesis

Hypoxy, oxidative stress, drusen, lipofuscine, inflammation→ VEGF-release→AMD



Age-related Macula Degeneration AMD
Symptoms

- Loss of central vision
- Increased probability of hip fractures

(within 4 years, fractures in **7.7%** with **AMD,** fractures in **4.9%** without **AMD**.

Age-related Macula Degeneration AMD
Incidence & Prevalence

Incidence:

Subjects, older than 49 years, within 10 years:

12.8% Dry AMD

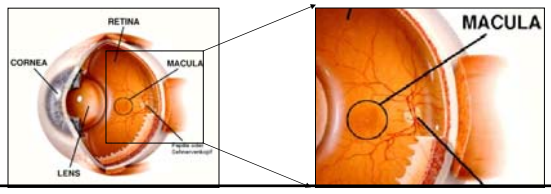
2.6% Wet AMD

Blue Mountains Eye Study, Beaver Dam Eye Study

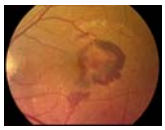
Prevalence:

Age	**Prevalence in %**
55-64 y	**0.21** %
65-74 y	**0.85** %
75-84 y	**4.6** %
85-94 y	**13.1** %

Pooled data N=14.000 (Beaver Dam-, Rotterdam-, und Blue Mountains Studien)

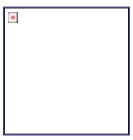


Age-related Macula Degeneration AMD
Diagnostics in Preventive Medicine



Fundus photography

Visual Acuity



Amsler Grid

Age-related Macula Degeneration AMD
Preventive Therapy

Drusen or Dry AMD:

Nutritive, antioxidative therapy with
•Lutein
•Zeaxanthin
•Omega-3-Acids
•Vit C and E
•Zinc

→Risk reduction by 25%* to 35%#

*AREDS-Research Group, J Nutr 2002, # Rotterdam-Study

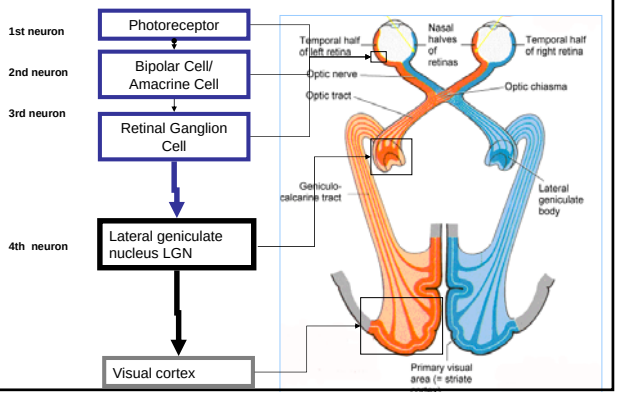
Directory of Lessons

Lesson 6

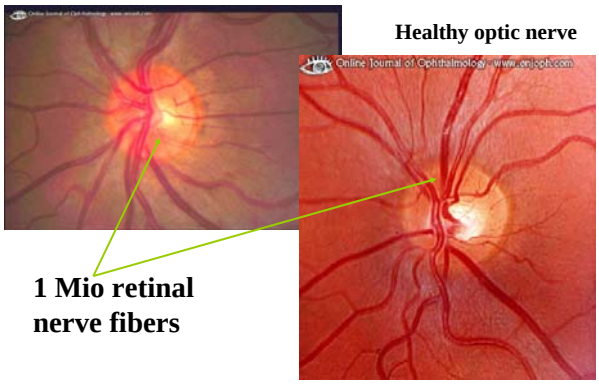
- **Important Diseases in Ophthalmological Preventive Medicine**
  - **Glaucoma**

Glaucoma
Pathogenesis

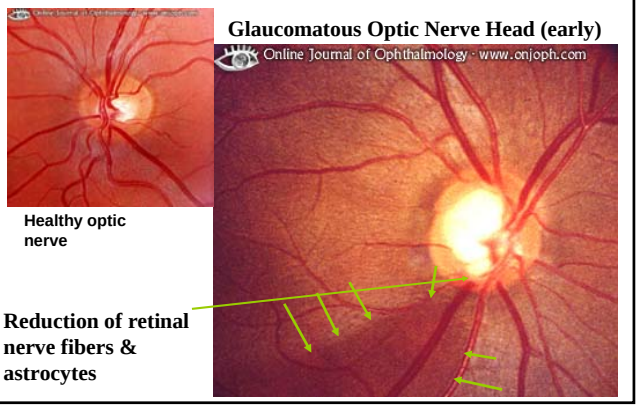
Glaucoma: Specific type of neurodegeneration of the visual pathway



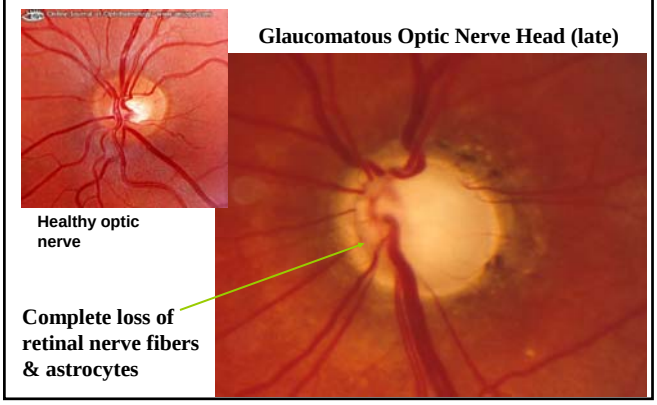
Glaucoma
Clinical Signs



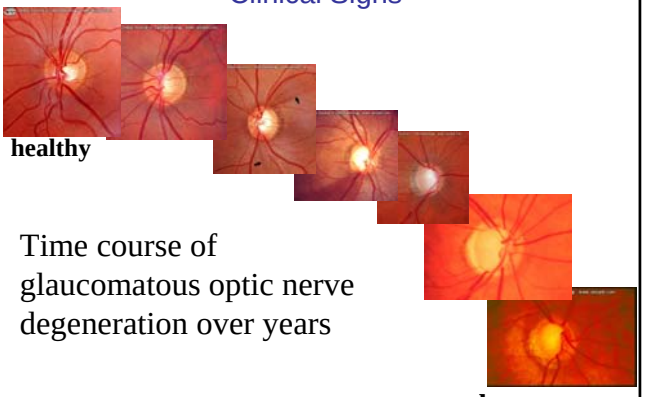
Glaucoma
Clinical Signs



Glaucoma
Clinical Signs

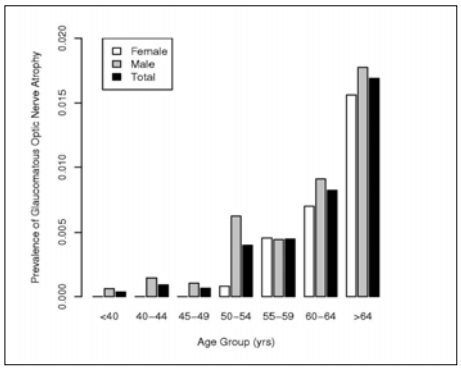


Glaucoma
Clinical Signs



Time course of glaucomatous optic nerve degeneration over years

Glaucoma
Prevalence



Klin Monbl Augenheilkd. 2010 Nov;227(11):905-11. **Prevalence of glaucomatous optic nerve atrophy among a working population in Germany diagnosed by a telemedical approach.** Adler W, Wärntges S, Lausen B, Michelson G.

Glaucoma
Diagnostics in Preventive Medicine

Fundus photography

Contactfree

Intraocular Pressure

Glaucoma
Preventive Therapy

Early Glaucoma:

•Decrease of intracular pressure with eye drops

•Nutritive, antioxidative therapy with
- •Lutein
- •Zeaxanthin
- •Omega-3-Acids
- •Vit C and E
- •Zinc

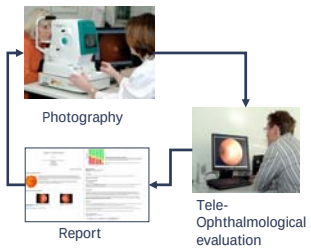
→Risk reduction

Directory of Lessons

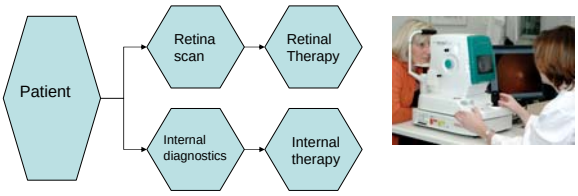
Lesson 8

Telemedical System Offering Ophthalmological Preventive Medicine for preventive care provider:

"Tele-OPM"



1)Parallel Processing of Multiple Disciplines in Preventive Medicine Improves Performance



2) Technical Needs

1. **Process Engine**
2. **Electronic Patient Chart**
3. **Telemedical Tools for**
   - Image upload
   - Telemedical evaluation of images and data
4. **Integration of multidisciplinary medical data**
5. **Generation of an multidisciplinary medical report, specified for**
   - medical doctors
   - patients

3) Benefits

- **Improvement of preventive medicine by**
  - Including retina check
  - Improving risk validity
- **Reduction of endorgan damages on a long run**

Telemedical System Offering Ophthalmological Preventive Medicine:
"Tele-OPM"

4) Realization
Method „Talkingeyes®" #1

- **Digital photography of the retina without mydriasis in rooms of GP**

- Upload of images at web-based patient chart
- Tele medical evaluation of retinal images &
- Computer-assisted calculation of arterio venous ratio
- Upload of evaluation at web-based patient chart
- Data on web-based patient chart part of therapy
- Quality assessment

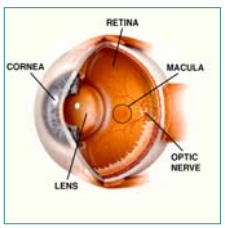
michelson@t-online.de

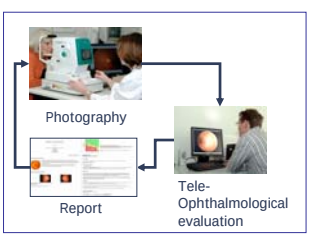
Directory of Lessons

Lesson 9

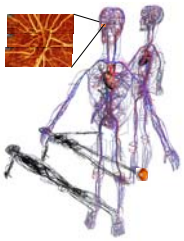
Conlusion

Ophthalmological Preventive Medicine OPM:

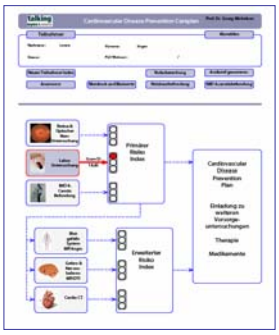




Summary 1
Interdisciplinary Prevention Includes Retina Check



„The Eye, Window to Brain and Heart"



michelson@t-online.de

Summary 2
Retina Check Improves Risk Assessment

Ophthalmological Preventive Medicine consists in looking for

- *Retinal Microangiopathy*
  - *Arterial Hypertension*
  - *Diabetes*
- *Age-related Maculadegeneration AMD*
- *Glaucoma*

Summary 3
Telemedical System *Tele-OPM* Provides Ophthalmological Preventive Medicine for Preventive Medicine Provider

Preventive Medicine Institution in Country X

Talkingeyes®-Technology

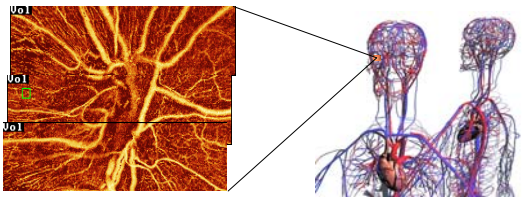
Photography

Tele-Ophthalmological evaluation

Report

Tele-Ophthalmogical Institute in Erlangen (Germany)

Summary 4
The Retina, Gateway to Medical Wisdom



Retina Flow Image

- **Literature**

- Benitez-Aguirre P, Craig ME, Sasongko MB, Jenkins AJ, Wong TY, Wang JJ, Cheung N, Donaghue KC (2011). Retinal vascular geometry predicts incident retinopathy in young people with type 1 diabetes: a prospective cohort study from adolescence. Diabetes Care 34: 1622–1627
- Cheung N, Sharrett AR, Klein R, Criqui MH, Islam FM, Macura KJ, Cotch MF, Klein BE, Wong TY (2007). Aortic distensibility and retinal arteriolar narrowing: the multi-ethnic study of atherosclerosis. Hypertension 50: 617–622
- Cuspidi C, Dell'Oro R, Grassi G (2009). Retinal arteriolar narrowing as marker of renal dysfunction: potential value and limitations. J Hypertens 27: 2162–2164
- Dahlof B, Sterukula S, Hansson L (1992). Hypertensive retinal vascular changes: relationship to left ventricular hypertrophy and arteriolar changes before and after treatment. Blood Press 1: 35–44
- De Silva DA, Manzano JJ, Liu EY, Woon FP, Wong WX, Chang HM, Chen C, Lindley RI, Wang JJ, Mitchell P, Wong TY, Wong MC (2011). Retinal microvascular changes and subsequent vascular events after ischemic stroke. Neurology 77: 896–903
- Duncan BB, Wong TY, Tyroler HA, Davis CE, Fuchs FD (2002). Hypertensive retinopathy and incident coronary heart disease in high risk men. Br J Ophthalmol 86: 1002–1006
- Ikram MK, de Jong FJ, Vingerling JR, Witteman JC, Hofman A, Breteler MM, de Jong PT (2004). Are retinal arteriolar or venular diameters associated with markers for cardiovascular disorders? The Rotterdam Study. Invest Ophthalmol Vis Sci 45: 2129–2134
- Kawasaki R, Tielsch JM, Wang JJ, Wong TY, Mitchell P, Tano Y, Tominaga M, Oizumi T, Daimon M, Kato T, Kawata S, Kayama T, Yamashita H (2008). The metabolic syndrome and retinal microvascular signs in a Japanese population: the Funagata study. Br J Ophthalmol 92: 161–166
- Kaushik S, Wang JJ, Wong TY, Flood V, Barclay A, Brand-Miller J, Mitchell P (2009). Glycemic index, retinal vascular caliber, and stroke mortality. Stroke 40: 206–212
- Kobayashi S, Okada K, Koide H, Bokura H, Yamaguchi S (1997). Subcortical silent brain infarction as a risk factor for clinical stroke. Stroke 28: 1932–1939
- Leung H, Wang JJ, Rochtchina E, Tan AG, Wong TY, Klein R, Hubbard LD, Mitchell P (2003). Relationships between Age, Blood Pressure, and Retinal Vessel Diameters in an Older Population. Invest Ophthalmol Vis Sci 44: 2900–2904
- Machemer R, Michelson G, Naumann G. Atlas of Ophthalmology. Online Multimedia Database. http://www.atlasophthalmology.com [Stand: 10.04.2012]
- Mark WJ, Strachan MD, John A, McKnight MD (2005). Improvement in Hypertensive Retinopathy after Treatment of Hypertension. N Engl J Med 352: e17
- McGeechan K, Liew G, Macaskill P, Irwig L, Klein R, Klein BE, Wang JJ, Mitchell P, Vingerling JR, de Jong PT, Witteman JC, Breteler MM, Shaw J, Zimmet P, Wong TY (2009). Prediction of incident stroke events based on retinal vessel caliber: A systematic review and individual-participant meta-analysis. Am J Epidemiol 170: 1323–1332
- Michelson G (2005). Talking Eyes-and-more. Biomed Tech 50: 218–226
- Michelson G, Laser M, Müller S, Weber F, Wärntges S (2011). Validation of telemedical fundus images from patients with retinopathy. Klin Monbl Augenheilkd 228: 234–238
- Michelson G, Groh M, Groh MJ, Balearu D, Harazny J, Horstmann R, Kolominsky-Rabas P (2005). Telemedical-supported screening of retinal vessels ("talking eyes"). Klin Monbl Augenheilkd 222: 319–325
- Sharrett AR, Hubbard LD, Cooper LS, Sorlie PD, Brothers RJ, Nieto FJ, Pinsky JL, Klein R (1999). Retinal arteriolar diameters and elevated blood pressure: the Atherosclerosis Risk in Communities Study. Am J Epidemiol 150: 263–270
- Sjølie AK, Klein R, Porta M, Orchard T, Fuller J, Parving HH, Bilous R, Chaturvedi N; DIRECT Programme Study Group (2008). Effect of candesartan on progression and regression of retinopathy in type 2 diabetes (DIRECT-Protect 2): a randomised placebo-controlled trial. Lancet 372: 1385–1393
- Smith W, Wang JJ, Wong TY, Rochtchina E, Klein R, Leeder SR, Mitchell P (2004). Retinal arteriolar narrowing is associated with 5-year incident severe hypertension: the Blue Mountains Eye Study. Hypertension 44: 442–447
- Tanabe Y, Kawasaki R, Wang JJ, Wong TY, Mitchell P, Daimon M, Oizumi T, Kato T, Kawata S, Kayama T, Yamashita H (2010). Retinal arteriolar narrowing predicts 5-year risk of hypertension in Japanese people: the Funagata study. Microcirculation 17: 94–102
- Wang JJ, Rochtchina E, Liew G, Tan AG, Wong TY, Leeder SR, Smith W, Shankar A, Mitchell P (2008). The long-term relation among retinal arteriolar narrowing, blood pressure, and incident severe hypertension. Am J Epidemiol 168: 80–88
- Wong TY, Klein R, Couper DJ, Cooper LS, Shahar E, Hubbard LD, Wofford MR, Sharrett AR (2001). Retinal microvascular abnormalities and incident strokes: the Atherosclerosis Risk in Communities Study. Lancet 358: 1134–1140
- Wong TY, Klein R, Sharrett AR, Nieto FJ, Boland LL, Couper DJ, Mosley TH, Klein BE, Hubbard LD, Szklo M (2002a). Retinal microvascular abnormalities and cognitive impairment in middle-aged persons: the Atherosclerosis Risk in Communities Study. Stroke 33: 1487–1492
- Wong TY, Klein R, Sharrett AR, Duncan BB, Couper DJ, Tielsch JM, Klein BE, Hubbard LD (2002b). Retinal arteriolar narrowing and risk of coronary heart disease in men and women: the Atherosclerosis Risk in Communities Study. JAMA 287: 1153–1159
- Wong TY, Klein R, Sharrett AR, Couper DJ, Klein BE, Liao DP, Hubbard LD, Mosley TH (2002c). Cerebral white matter lesion, retinopathy and incident clinical stroke. JAMA 288: 67–74
- Wong TY, Mosley TH Jr, Klein R, Klein BE, Sharrett AR, Couper DJ, Hubbard LD; Atherosclerosis Risk in Communities Study (2003a). Retinal microvascular changes and MRI signs of cerebral atrophy in healthy, middle-aged people. Neurology 61: 806–811
- Wong TY, Klein R, Nieto FJ, Klein BE, Sharrett AR, Meuer SM, Hubbard LD, Tielsch JM (2003b). Retinal microvascular abnormalities and 10-year cardiovascular mortality: a population-based case-control study. Ophthalmology 110: 933–940
- Wong TY, Klein R, Sharrett AR, Duncan BB, Couper DJ, Klein BE, Hubbard LD, Nieto FJ; Atherosclerosis Risk in Communities Study (2004a). Retinal arteriolar diameters and risk for hypertension. Ann Intern Med 140: 248–255
- Wong TY, Duncan BB, Golden SH, Klein R, Couper DJ, Klein BE, Hubbard LD, Sharrett AR, Schmidt MI (2004b). Associations between the Metabolic Syndrome and Retinal Microvascular Signs: The Atherosclerosis Risk in Communities Study. Invest Ophthalmol Vis Sci 45: 2949–2954
- Wong TY, Rosamond W, Chang PP, Couper DJ, Sharrett AR, Hubbard LD, Folsom AR, Klein R (2005). Retinopathy and the risk of congestive heart failure. JAMA 293: 63–69
- Yatsuya H, Folsom AR, Wong TY, Klein R, Klein BE, Sharrett AR; ARIC Study Investigators (2010). Retinal microvascular abnormalities and risk of lacunar stroke: Atherosclerosis Risk in Communities Study. Stroke 41: 1349–1355