# Microvascular complications in the metabolic syndrome

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## Disclosures

- Speaker: Astra Zeneca, Abbott Nutrition, Novartis Oncology, Novartis Pharma, Novo Nordisk, Merck Sharp & Dohme, Roche, Glaxo SmithKline, Sanofi Aventis, Bayer, Boehringer Ingelheim, Janssen, Pfizer
- Advisory Board: Novartis Oncology, Sanofi Aventis, Astra Zeneca, Novo Nordisk, Stendhal, Pfizer, Janssen
- Clinical Investigation: Astra Zeneca, Novartis Pharma Logistics Inc., Merck Sharp & Dohme, Glaxo SmithKline, Organon, Boehringer Ingelheim, Roche, Novo Nordisk

## Agenda

- What is the risk of microvascular complications in MS (with or without diabetes)? Brain? Skin?
- Is there a common pathophysiology?
- What can we do about it?

## Initial thoughts…

- Some type 2 diabetics have microvascular complications when diagnosed
- Usual explanation is a delay in diagnosis
- However, it is not unusual to see recently diagnosed T2DM with very mild hyperglycemia with microvascular complications
- Can prediabetes or metabolic syndrome initiate microvascular complications?

## Initial thoughts… (2)

- It has been known for several years that hypertension may accelerate progression of microvascular disease in T2DM
- However, it is controversial if HTN per se or insulin resistance may lead to microvascular complications independent of T2DM
- Cutoff points for diagnosis of DM are based on the threshold where diabetic retinopathy increases

## Retinopathy

## MS and diabetic retinopathy

| Author, year | Study design | Study population | Criteria used | Results |
|---|---|---|---|---|
| Raman, 2010 | Population based cross sectional | 1414 T2DM in India | IDF | No difference in DR in those with or without MS |
| Abdul-Ghani, 2006 | Primary care, case control study | 415 T2DM in Israel | NCEP-III and WHO | MS is a significant risk factor for DR OR 3.42 (1.2-9.87) |
| Metascreen Writing, 2006 | Multicentre cross sectional | 7859 T2DM and 638 T1DM in Italy | AHA and IDF | OR 1.36 (p=0.16) in T1DM and 1.41 (p<0.001) in T2DM |
| Costa, 2004 | Hospital based cross sectional | 548 T2DM | WHO | OR 3.61 (1.75-7.46). Risk increases parallel to number of components of MS |
| Isomaa, 2001 | Clinic based, case control study | 170 T2DM in Finland | WHO | No difference |

Poh S. Diab Res Clin Pract. 2016;113:86

## Patients without DM

## MS and retinopathy in China

**Table 3** Prevalence of retinopathy in different groups of participants

| Group | Retinopathy (n) | Prevalence (%) |
|---|---|---|
| All diabetics | 55 | 11.79 |
| Known diabetes | 34 | 18.18 |
| Newly detected diabetes | 21 | 7.72 |
| Non-diabetics | 19 | 3.25 |
| With MS | 48 | 9.64 |
| Without MS | 26 | 3.91 |
| All subjects | 74 | 6.36 |

MS, metabolic syndrome.

Liu L. BMJ Open. 2015;5:e008855

## Inter99 Eye Study in Denmark

| | Included participants without diabetes ($n$ = 711) |
|---|---|
| Age, years | 46.9 (7.6) |
| Men/women, % | 47/53 |
| Danish nationality, % | 97 |
| Body mass index, kg/m$^2$ | 27.0 (4.8) |
| Systolic blood pressure, mmHg | 131 (16.5) |
| Diastolic blood pressure, mmHg | 83 (10.8) |
| Hypertension (> 140/90 mmHg), % | 41 |
| Smoking daily, % | 37 |
| Total cholesterol, mM | 5.79 (1.23) |
| Low-density lipoprotein, mM | 3.7 (1.0) |
| Triglycerides, mM | 1.2 (0.9) |
| Low HDL cholesterol[§], % | 24 |
| $HbA_{1c}$, % | 5.83 (0.41) |
| FPG, mM | 5.5 (0.7) |
| Normal glucose tolerance, % | 62 |
| Isolated impaired fasting glucose (IFG), % | 8.0 |
| Isolated impaired glucose tolerance (IGT), % | 21 |
| Combined IFG + IGT, % | 8.9 |
| Lens fluorescence, mg f-eq/ml | 524 (266) |
| Retinopathy, ETDRS ≥15, % | 8.3% |
| Retinopathy, ETDRS ≥35, % | 1.1% |

Any retinopathy

Mild retinopathy or worse

Munch IG. Acta Ophtalmologica. 2012;90:613

## Inter99 Eye Study

- Risk of retinopathy had a positive association with:
  - Systolic blood pressure
    - OR 3.37 (1.4-8.1) if SBP >160 mm Hg
  - Abdominal circumference
- No association with:
  - Diastolic blood pressure
  - Waist hip ratio
  - Lipid profile
  - Age

Munch IG. Acta Ophtalmologica. 2012;90:613

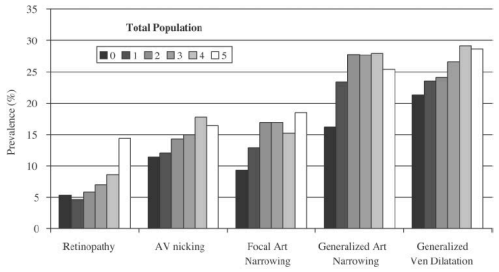
## Atherosclerosis Risk in Communities (ARIC)

| | | Retinopathy | | Arteriovenous Nicking | | Focal Arteriolar Narrowing | | Generalized Arteriolar Narrowing | | Generalized Venular Dilatation | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Metabolic Syndrome | *N* | % | OR (95% CI) | % | OR (95% CI) | % | OR (95% CI) | % | OR (95% CI) | % | OR (95% CI) |
| All participants | | | | | | | | | | | |
| MS present | 4223 | 8.8 | 1.68 (1.44, 1.96) | 16.4 | 1.30 (1.16, 1.45) | 17.2 | 1.24 (1.1, 1.38) | 27.5 | 1.23 (1.12, 1.35) | 27.4 | 1.30 (1.18, 1.48) |
| MS absent | 7042 | 5.1 | 1.00 | 12.8 | 1.00 | 13.5 | 1.00 | 23.6 | 1.00 | 24.9 | 1.00 |
| Participants without diabetes | | | | | | | | | | | |
| MS present | 2928 | 5.6 | 1.22 (1.00, 1.49) | 16.0 | 1.28 (1.13, 1.45) | 17.8 | 1.31 (1.16, 1.48) | 28.6 | 1.27 (1.15, 1.41) | 25.6 | 1.24 (1.11, 1.38) |
| MS absent | 5529 | 3.6 | 1.00 | 12.7 | 1.00 | 13.5 | 1.00 | 23.0 | 1.00 | 25.0 | 1.00 |
| Participants without hypertension | | | | | | | | | | | |
| MS present | 1599 | 6.3 | 1.46 (1.14, 1.86) | 13.4 | 1.25 (1.05, 1.48) | 12.9 | 1.26 (1.05, 1.51) | 21.4 | 1.10 (0.96, 1.28) | 27.9 | 1.34 (1.17, 1.54) |
| MS absent | 5569 | 4.3 | 1.00 | 12.8 | 1.00 | 13.2 | 1.00 | 23.7 | 1.00 | 25.2 | 1.00 |
| Participants without diabetes or hypertension | | | | | | | | | | | |
| MS present | 1191 | 4.2 | 1.05 (0.76, 1.45) | 13.1 | 1.23 (1.01, 1.49) | 14.1 | 1.40 (1.16, 1.70) | 23.0 | 1.19 (1.01, 1.39) | 25.8 | 1.25 (1.07, 1.46) |
| MS absent | 4965 | 4.0 | 1.00 | 10.9 | 1.00 | 10.1 | 1.00 | 20.0 | 1.00 | 23.3 | 1.00 |

MS, metabolic syndrome.
* Adjusted for age, gender, race, field center, education, cigarette smoking, and alcohol consumption status.

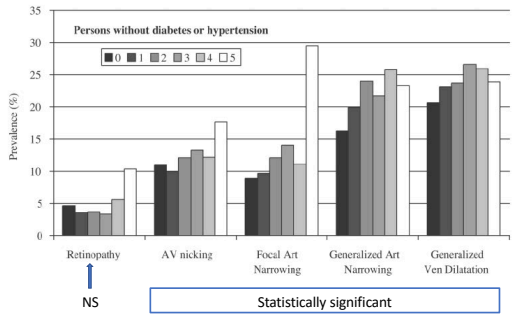
Tien YW. Ophtalmol Vis Sci. 2004;45:2949

## Atherosclerosis Risk in Communities (ARIC)



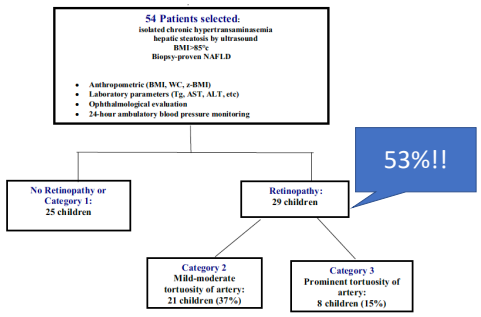

Tien YW. Ophtalmol Vis Sci. 2004;45:2949

## ARIC




Tien YW. Ophtalmol Vis Sci. 2004;45:2949

## Pediatric patients with NAFLD




Liccardo D. J Gastroenterol. 2015;50:903

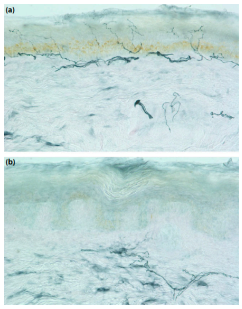
## Pediatric patients with NAFLD

| | NoR (category 1) ($n = 25$) | R ($n = 29$) | $p$ |
|---|---|---|---|
| Age (years) | 11.56 ± 2.65 | 10.91 ± 3.10 | 0.89 |
| BMI (kg/m$^2$) | 27.76 ± 5.47 | 30.33 ± 6,50 | 0.18 |
| WC (cm) | 89.24 ± 11.33 | 83.80 ± 21.68 | 0.63 |
| Chol-T (mg/dl) | 158.84 ± 27.53 | 153.72 ± 24.29 | 0.89 |
| HDL(mg/dl) | 46.40 ± 12.63 | 45.38 ± 9.66 | 0.35 |
| LDL(mg/dl) | 95.88 ± 12.63 | 92.21 ± 21.35 | 0.56 |
| Tg (mg/dl) | 90.20 ± 36.47 | 105.57 ± 42.47 | 0.04* |
| AST (U/l) | 30.12 ± 10.91 | 28.86 ± 9.99 | 0.42 |
| ALT(U/l) | 37.60 ± 20.01 | 38.10 ± 18.93 | 0.73 |
| GGT(U/l) | 18.76 ± 10.96 | 16.33 ± 7.24 | 0.74 |
| Fasting plasma glucose (mg/dl) | 82.56 ± 9.43 | 82.59 ± 8.48 | 0.13 |
| Fasting plasma gluc-120 | 96.38 ± 16.95 | 99.38 ± 12.79 | 0.10 |
| Insulin | 12.97 ± 3.50 | 17.20 ± 7.54 | 0.02* |
| Insulin-120 | 73.71 ± 75.96 | 90.72 ± 52.53 | 0.33 |
| HOMA-IR | 2.76 ± 0.82 | 3.37 ± 1.58 | 0.04* |
| CIMT-right (mm) | 0.46 ± 0.08 | 0.48 ± 0.06 | 0.66 |
| CIMT-left (mm) | 0.47 ± 0.05 | 0.49 ± 0.10 | 0.42 |

Liccardo D. J Gastroenterol. 2015;50:903

## Neuropathy

## Intraepidermal nerve fiber density




Control

Metabolic syndrome

Stino AM. J Diab Invest. 2017;8:646

## KORA F4: clinical sensitive neuropathy in 1100 persons

| | Clinical DSPN | | | |
|---|---|---|---|---|
| | No | Yes | OR | 95% CI |
| Oral glucose tolerance status | | | | |
| NGT | 513 | 64 | 1.00 | Reference |
| Prediabetes (total) | 243 | 41 | 1.22 | 0.78–1.90 |
| i-IFG | 52 | 3 | 0.33 | 0.10–1.13 |
| i-IGT | 156 | 27 | 1.26 | 0.76–2.08 |
| IFG-IGT | 35 | 11 | 2.82 | 1.29–6.10 |
| Diabetes (total) | 190 | 49 | 1.54 | 1.01–2.42 |
| Known diabetes | 138 | 39 | 1.77 | 1.10–2.87 |
| Undiagnosed diabetes | 52 | 10 | 1.22 | 0.57–2.61 |

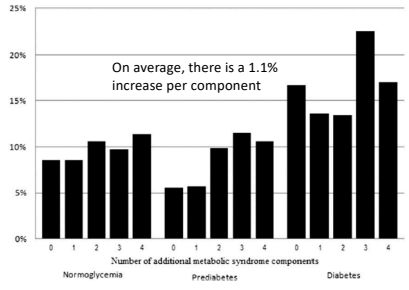
Bongaerts BWC. Diabetes Care. 2012;35:1891

## Neuropathy

- In a case series of 187 patients with idiopathic neuropathy:
  - 45% glucose intolerance
  - 15% had DM
  - Compared to a prevalence of age adjusted glucose intolerance of 15%
- Could it be the other way around?
  - Neuropathic pain that limits physical activity and therefore increases the risk of obesity and glucose intolerance?

Smith AG. The Neurologist. 2008;14:23

## Neuropathy and number of components of MS: Health ABC cohort




Callaghan BC. Diabetes Care. 2016;39:801

## MS and neuropathy: mechanisms

- Increased oxidative stress
- Increased formation of diacylglycerol (DAG) and subsequent activation of protein kinase C
- Increased flux through polyol pathway
- Endothelial dysfunction contribute to hypoxia

## Neuropathy in MS without DM

- Brazilian cohort in MS patients without DM with grade II or grade III obesity
- 218 patients
- 11% prevalence of painful peripheral neuropathy

**TABLE 3** Multivariate Poisson regression, in order to evaluate which factors were independently associated to the occurrence of PPN in the sample of degree II and III obesity patients with MetS and without DM.

| Variables | Model | |
|---|---|---|
| | PR (95CI) | p-value |
| Low HDL-c | 4.12 (1.02 – 16.7) | 0.047* |
| LDL-c | 1.01 (1.00 – 1.02) | 0.118 |
| Triglycerides (mg/dL) | 1.00 (0.99 – 1.01) | 0.239 |

Nienov OH. Rev Assoc Med Bras. 2017;63:324

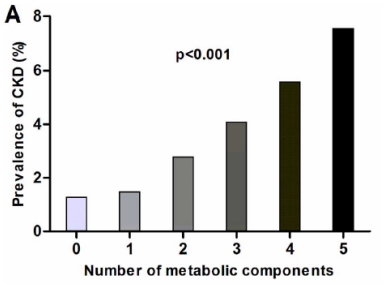
## MS and neuropathy: low HDL

- Mechanisms:
  - In vitro studies have shown that HDL can be captured by injured distal axons and used for regeneration of these fibers
  - No in vivo studies
  - Exercise is associated with better autonomic function and could prevent the decrease of nerve function related to aging

Nienov OH. Rev Assoc Med Bras. 2017;63:324

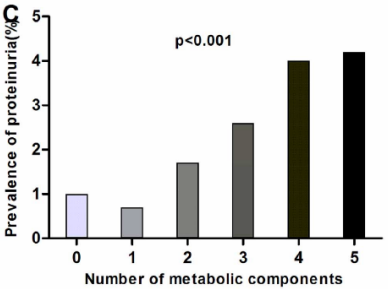
# Nephropathy

## MS and CKD (microalbuminuria or GFR <60) in China



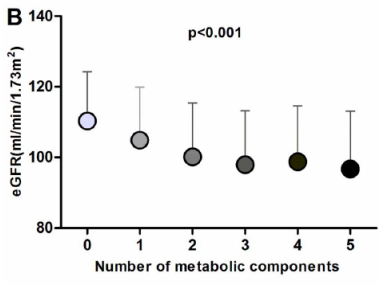

Chen J. Clin Chem .2017;470:103

## MS and CKD in China




Chen J. Clin Chem .2017;470:103

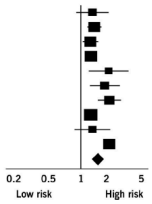
## MS and CKD in China




Chen J. Clin Chem .2017;470:103

## Meta-analysis: MS and CKD (GFR <60 cc/min)

| Study name | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|
| Kitiyakara 2007 | 1.36 | 0.89 | 2.09 | 1.40 | 0.16 |
| Kurella 2005 | 1.43 | 1.18 | 1.73 | 3.66 | 0.00 |
| Lucove 2008 | 1.29 | 1.05 | 1.59 | 2.41 | 0.02 |
| Luk 2008 | 1.31 | 1.12 | 1.54 | 3.32 | 0.00 |
| Ninomiya 2006 | 2.08 | 1.23 | 3.52 | 2.73 | 0.01 |
| Rashidi 2007 | 1.88 | 1.26 | 2.80 | 3.10 | 0.00 |
| Ryu 2009 | 2.12 | 1.56 | 2.89 | 4.75 | 0.00 |
| Sun 2010 | 1.30 | 1.24 | 1.36 | 11.13 | 0.00 |
| Tozawa 2007 | 1.36 | 0.84 | 2.19 | 1.26 | 0.21 |
| Watanabe 2010 | 2.12 | 1.80 | 2.49 | 9.12 | 0.00 |
| | 1.55 | 1.34 | 1.80 | 5.88 | 0.00 |




Thomas G. Clin J Am Soc Nephrol. 2011;6:2364

## Meta-analysis: Individual components and risk of CKD

| Components of Metabolic Syndrome | Number of Studies/Patients | Odds Ratio (95% CI) | *P* |
|---|---|---|---|
| Elevated blood pressure | 8/26,405 | 1.61 (1.29, 2.01) | <0.01 |
| Impaired fasting glucose | 8/26,405 | 1.14 (1.03, 1.26) | <0.01 |
| Elevated triglycerides | 8/28,721 | 1.27 (1.11, 1.46) | <0.01 |
| Low HDL cholesterol | 8/26,632 | 1.23 (1.12, 1.36) | <0.01 |
| Obesity | 9/28,897 | 1.19 (1.05, 1.34) | <0.01 |

Thomas G. Clin J Am Soc Nephrol. 2011;6:2364

## Renal changes in MS

- Tubular atrophy
- Interstitial fibrosis
- Arterial and arteriolar sclerosis
  - Elevated resistive indexes in intrarenal interlobar arteries
- In early stages, MS stimulated microvascular proliferation in the kidney
- Later on, these newly generated vessels become more tortuous
- Inflammation may mediate renal fibrosis and glomerulosclerosis

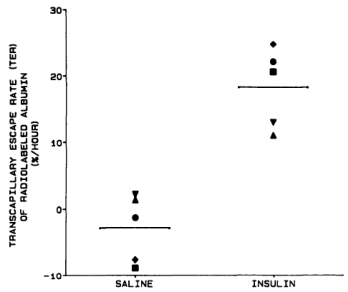
Zhang X. Translational Res. 2016; online 22 dec 2016.

## Renal effects of hyperinsulinemia

- Glomerular hyperfiltration (vasodilation)
- Endothelial dysfunction
- Increased vascular permeability
- Short term insulin infusion in non-diabetic subjects leads to urinary albumin excretion
- Albumin in the tubular lumen leads to tubulointerstitial injury and fibrosis

Zhang X. Translational Res. 2016; online 22 dec 2016.

## Transcapillary escape rate of albumin after insulin infusion

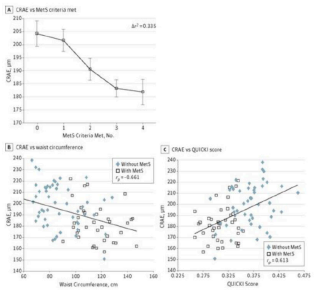



Nestler JE. Diabetes. 1990;39:1212

## Other tissues

## Brain: early changes in adolescents

## Retinal vessel and MS in adolescents



CRAE = central retinal arteriolar equivalent

Yau PL. JAMA Pediatr. 2014;168:e142815

## White matter changes

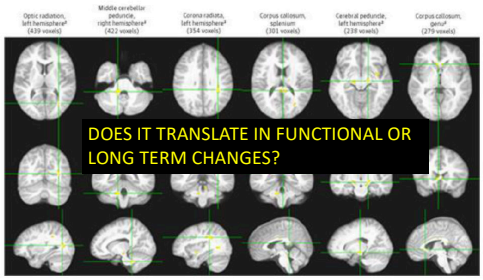
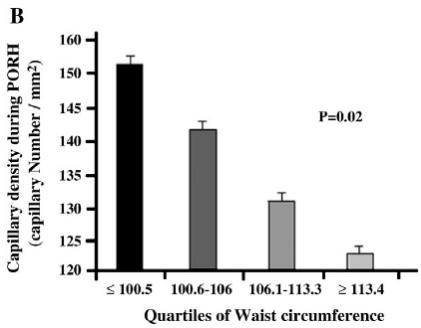


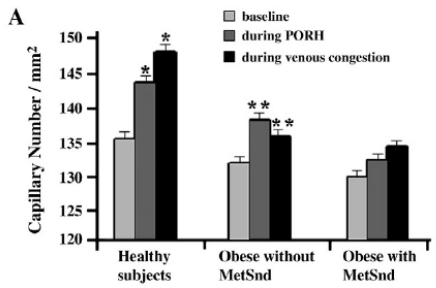

**Figure 3. Six Largest White Matter Clusters All Demonstrating Significant Positive Association Between Fractional Anisotropy and Central Retinal Arteriolar Equivalent Independent of Age and After Controlling for Central Retinal Venular Equivalent**

Yau PL. JAMA Pediatr. 2014;168:e142815

## Skin




Francischetti EA. Microvascular Res. 2011;81:325



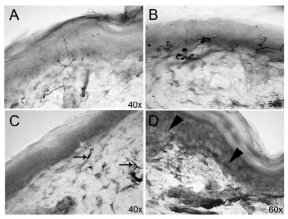

4x increase in PORH (post occlusive reactive hyperemia) in healthy subjects vs MS

Francischetti EA. Microvascular Res. 2011;81:325

## What can we do about it?

## IGTN

- Lifestyle modification in patients with prediabetes:
  - Improved intraepithelial nerve fiber density demonstrated by biopsy
  - Not associated with pain improvement measured by VAS




Smith AG. Diabetes Care. 2006;29:1294

## TopCSPN

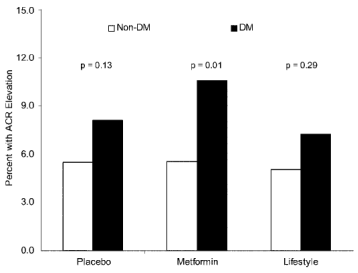
- Topiramate as  a Disease Altering Therapy for Crytogenic Sensory Neuropathy
- Patients with obesity, sensory neuropathy and metabolic syndrome
- Ongoing RCT topiramate 100 mg vs placebo
- Primary outcome:
  - Intraepithelial nerve fiber density
  - Norfolk Quality of Life– Diabetic Neuropathy Scale

## DPP: elevated ACR at baseline

| End of study status | Placebo | Metformin | Intensive lifestyle modifications |
|---|---|---|---|
| Resolved elevated ACR | 48% | 56% | 64% |
| Remained with elevated ACR | 52% | 44% | 35% |

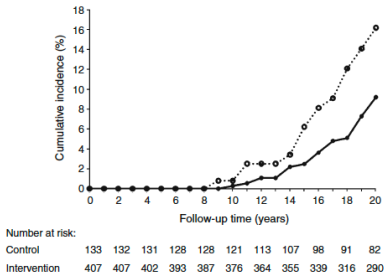
DPP Research Group. Diabetes Care. 2009;32:720

## DPP: albuminuria




DPP Research Group. Diabetes Care. 2009;32:720

## Da-Qing: long term microvascular complications




Number at risk:

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Control | 133 | 132 | 131 | 128 | 128 | 121 | 113 | 107 | 98 | 91 | 82 |
| Intervention | 407 | 407 | 402 | 393 | 387 | 376 | 364 | 355 | 339 | 316 | 290 |

Gong Q. Diabetologia. 2011;54:300

## Da-Qing: incidence of severe retinopathy

| Follow-up time (years) | Intervention group | | | | Control group | | | | Hazard rate ratio (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| | No. of cases | No. of participants | Person-years | Incidence (/1,000 person-years) | No. of cases | No. of participants | Person-years | Incidence (/1,000 person-years) | |
| 0–9.9 | 0 | 439 | 4,067 | – | 1 | 136 | 1,306 | 0.77 | – |
| 10–14.9 | 8 | 378 | 1,796 | 4.45 | 3 | 121 | 549 | 5.46 | 0.82 (0.22–3.10) |
| 15–20 | 23 | 348 | 1,579 | 14.6 | 13 | 104 | 454 | 28.6 | 0.51 (0.26–1.01) |
| Total | 31 | 439 | 7,442 | 4.2 | 17 | 136 | 2,301 | 7.4 | 0.53 (0.29–0.99)[a, b] |

$P_{trend}$<0.0001 for follow-up time

All patients who developed retinopathy progressed to DM!

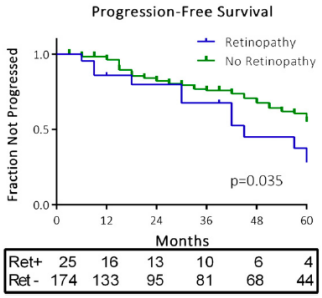
Gong Q. Diabetologia. 2011;54:300

## Early Diabetes Intervention Program (EDIP)

- Included patients with fasting glucose between 105 and 140 mg/dl
- Acarbose vs placebo
- 194 patients
- Evaluated by retinal photography
- 12.4% had retinopathy
- 8.4% with neuropathy
- 4.5% with nephropathy

Patel YR. J Diab Comp. 2017

## EDIP: Retinopathy predicts glucose progression




RR for progression is 2.02 (1.05-3.89), although in multivariate analysis adjusted for age and fasting glucose is not statistically significant

Patel YR. J Diab Comp. 2017

## Should we screen all patients with MS for microvascular complications?

- Most of these microvascular complications are subclinical
- Patients that progressed to more severe lesions are usually those who develop T2DM
  - Recently diagnosed patients should be screened
- The higher the number of MS components, risk of complications is higher
  - Screening may be warranted in those with 4 or 5 traits
- Screening programs in patients with MS without DM have not shown to decrease complications related endpoints (laser photocoagulation, ESRD, etc.)

## Take home messages

- MS is associated with a higher risk of microvascular complications not only in classical tissues but also on vasculature, brain and skin
- Most of these complications are subclinical
- Patients that develop severe complications are those who progress to DM
- Intervention with lifestyle modifications and treatment of MS components may delay the onset and progression of microvascular complications

# Questions…

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