Advances in the Diagnosis and Management of the Diabetic Triopathy

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Weil Cornell Medicine-Qatar
& Weill Cornell Medicine in NY
Speaker:

Rayaz A. Malik, MD

- Has disclosed that he serves on the Speaker’s Bureau for Pfizer and Lilly

- Will not be discussing the off-label or investigational use of products
Diabetic Triopathy: Unholy Trinity
Diabetic Retinopathy
Blindness
25 patients/week.

Diabetic Nephropathy
Leading cause of end-stage renal disease

Diabetic Neuropathy
107 amputations/week

Conversation in 2001
With Prof Nathan Efron about a Corneal confocal microscope!
Corneal Confocal Microscopy

- Rapid (2 min)
- Non-invasive (in vivo)
- Reiterative

- Images Corneal Structure.
Corneal tomography
Corneal confocal microscopy: a non-invasive surrogate of nerve fibre damage and repair in diabetic patients

R. A. Malik¹, P. Kallinikos², C.A. Abbott¹, C.H.M. van Schie¹, P. Morgan², N. Efron², A. J. M. Boulton¹

Corneal Confocal Microscopy Detects Neuropathy in Subjects With Impaired Glucose Tolerance

Asghar, Petropoulos et al. Diabetes Care 2014; 37: 2643-46
## T1DM- Children

<table>
<thead>
<tr>
<th></th>
<th>Controls (mean± SD)</th>
<th>T1DM (mean± SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>52</td>
<td>84</td>
<td>-</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>13.3±2.99</td>
<td>14.64±2.39</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Duration of Diabetes (years)</strong></td>
<td>NA</td>
<td>8.74±2.62</td>
<td>-</td>
</tr>
<tr>
<td><strong>HbA1C (%)</strong></td>
<td>NA</td>
<td>8.92±1.75</td>
<td>-</td>
</tr>
<tr>
<td><strong>Corneal nerve fibre Density (no./mm²)</strong></td>
<td>31.79±7.79</td>
<td>31.07±7.51</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Corneal nerve branch Density (no./mm²)</strong></td>
<td><strong>87.83±39.09</strong></td>
<td><strong>69.65±30</strong></td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Corneal nerve fibre length (mm/mm²)</strong></td>
<td><strong>25.04±6.12</strong></td>
<td><strong>22.66±4.75</strong></td>
<td>0.01</td>
</tr>
</tbody>
</table>

Ferdousi et al. 2015
T1DM- Children

Ferdousi et al. 2015
Diabetic Neuropathy: Risk Factors

- Hypertension: 1.57
- Smoking: 1.38
- HbA1c: 1.48
- Change in HbA1c: 1.36
- Diabetes duration: 1.40
- BMI: 1.27
- Triglycerides: 1.21
- Total cholesterol: 1.15

Hypertension

- Hypertension
- Smoking
- HbA1c
- Change in HbA1c
- Diabetes duration
- BMI
- Triglycerides
- Total cholesterol

ACEi Neuropathy

DEMAND study

- 380 hypertensive type 2 diabetic patients without nephropathy over ~4 yrs.

Manidipine (10 mg/day) plus Delapril (30 mg/day)
Delapril (30 mg/day)
Placebo

Ruggenenti P et al. Hypertension 2011; 58: 776-783
Neuropathy ↓40%

Ruggenenti P et al. Hypertension 2011; 58: 776-783
Triglycerides

Hypertension

Smoking

HbA1c

Change in HbA1c

Diabetes duration

BMI

Triglycerides

Total cholesterol

FIELD study

<table>
<thead>
<tr>
<th>Event</th>
<th>Fenofibrate (n=4895)</th>
<th>Placebo (n=4900)</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First amputation*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>28 (0.6%)</td>
<td>52 (1.1%)</td>
<td>0.54 (0.34–0.85)</td>
<td>0.007</td>
</tr>
<tr>
<td>Major</td>
<td>24 (0.5%)</td>
<td>26 (0.5%)</td>
<td>0.93 (0.53–1.62)</td>
<td>0.79</td>
</tr>
<tr>
<td>Minor, without large-vessel disease</td>
<td>18 (0.4%)</td>
<td>34 (0.7%)</td>
<td>0.53 (0.30–0.94)</td>
<td>0.027</td>
</tr>
<tr>
<td>Major or minor, with large-vessel</td>
<td>34 (0.7%)</td>
<td>42 (0.9%)</td>
<td>0.81 (0.52–1.28)</td>
<td>0.37</td>
</tr>
<tr>
<td>disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any amputation</td>
<td>45 (0.9%)</td>
<td>70 (1.4%)</td>
<td>0.64 (0.44–0.94)</td>
<td>0.02</td>
</tr>
<tr>
<td>Multiple events analysis†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All amputations</td>
<td>73</td>
<td>117</td>
<td>0.63 (0.40–0.97)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

PPARα: an emerging therapeutic target in diabetic microvascular damage

LIPID independent Anti-inflammatory, Anti-fibrotic Anti-oxidant ARI’s

Painful Neuropathy
Is pain due to DSPN confirmed?

Yes
Assess comorbidities, potential for AEs, drug interactions, costs to select initial therapy from the 3 choices below

- Voltage gated α2-δ ligand (pregabalin, gabapentin)
- Serotonin-norepinephrine reuptake inhibitor (duloxetine, venlafaxine)
- Tricyclic Antidepressant (Nortriptiline/Desipramine)

No clinically meaningful effect

- a. Switch to another agent from above
- b. Try combining agents from above
- c. May add Tapentadol or Tramadol if a and b fail

No clinically meaningful effect/Not tolerated

Refer to Pain Clinic

No/Not sure
Refer to Neurology/Pain Clinic
“Sometimes obvious conditions and treatments are the most difficult to grasp”
Vit D and DPN

OR for Painful Diabetic Neuropathy:
Vit D deficiency (<20ng/ml): 9.8 (95% CI 2.2-76.4), P<0.003
Vitamin D insufficiency (<30ng/ml): 4.4 (95% CI 1.1-19.8), P=0.03

Alam et al. Pain 2015 Under review
Oral Vit D

D3 2000U daily for 3 months

+67.4%  
P=0.001

-48.5%  
P=0.001

25 OHD  
VAS/100

IM Vitamin D

D3 600,000 IU IM: FU 20 weeks

Basit et al. 2015 BMJ Open In Press
Vitamin D protocol

Target to minimize symptoms, metabolic, cardiovascular and cancer risk: 60-100ng/ml.

25 OHD
<20ng/ml: Severely Vit D deficient
20-40 ng/ml: Moderately Vit D deficient
40-60 ng/ml: Vit D deficient

Loading dose
Colecalciferol (vitamin D₃): 40,000 IU daily for 14 days (560,000 IU).

Maintenance
Colecalciferol (vitamin D₃): 20-40,000 IU once weekly.

Repeat vitamin D & calcium after 3 months

If <50ng/ml
If 60-100 ng/ml

Note: Threshold for Vit D toxicity 40000-100000U daily for ~8 weeks (2.5-4 M IU)
Diabetic Retinopathy
Effect of candesartan on prevention (DIRECT-Prevent 1) and progression (DIRECT-Protect 1) of retinopathy in type 1 diabetes: randomised, placebo-controlled trials

1421 T1DM Candesartan 16mg v placebo over 5 years

<table>
<thead>
<tr>
<th></th>
<th>DIRECT-Prevent 1</th>
<th></th>
<th>DIRECT-Protect 1</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Candesartan</td>
<td>Placebo</td>
<td>Candesartan</td>
<td>Placebo</td>
</tr>
<tr>
<td>(N=711)</td>
<td>(N=710)</td>
<td></td>
<td>(N=951)</td>
<td>(N=954)</td>
</tr>
<tr>
<td>Men</td>
<td>413 (58%)</td>
<td>392 (55%)</td>
<td>538 (57%)</td>
<td>553 (58%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>29.6 (8.0)</td>
<td>29.9 (8.1)</td>
<td>31.5 (8.5)</td>
<td>31.9 (8.5)</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>6.6 (3.9)</td>
<td>6.8 (3.9)</td>
<td>10.9 (4.3)</td>
<td>11.0 (4.3)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>690 (57%)</td>
<td>685 (97%)</td>
<td>928 (98%)</td>
<td>943 (99%)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.0 (1.7)</td>
<td>8.2 (1.7)</td>
<td>8.5 (1.6)</td>
<td>8.5 (1.6)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>116 (9.5)</td>
<td>116 (9.6)</td>
<td>117 (9.6)</td>
<td>117 (9.8)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>72 (6.9)</td>
<td>72 (7.3)</td>
<td>74 (6.5)</td>
<td>73 (6.9)</td>
</tr>
</tbody>
</table>

Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial

9795 T2DM Fenofibrate 200mg v placebo over 5 years

Keech et al Lancet 2007; 370: 1687-97
Effects of Medical Therapies on Retinopathy Progression in Type 2 Diabetes

The ACCORD Study Group and ACCORD Eye Study Group

3-step progression on ETDRS or Laser photocoagulation or Vitrectomy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Progression of Diabetic Retinopathy</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycemia therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive &lt;6%</td>
<td>0.67 (0.51–0.87)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Standard 7–7.9%</td>
<td>104/1429 (7.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia therapy†</td>
<td>149/1427 (10.4)</td>
<td>0.60 (0.42–0.87)</td>
<td>0.006</td>
</tr>
<tr>
<td>With fenofibrate</td>
<td>52/806 (6.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With placebo</td>
<td>80/787 (10.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive &lt;120</td>
<td>67/647 (10.4)</td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>Standard &lt;140</td>
<td>54/616 (8.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diabetic Nephropathy

- α-blocker
- Central
- Thiazide-D
- ACEi
- CCB
- ARB
- Loop-D
- Spironolactone
- B-blockers
Super doses-SMART trial

- 269 patients (53.9% diabetic nephropathy) with persistent proteinuria (1 g/d) despite 7 wk of treatment with Candesartan (16 mg/d).
- Randomized to: 16, 64, or 128 mg/d Candesartan for 30 wk.
- Median urinary protein excretion 2.66 g/d.
- Proteinuria: 16 mg/d (-17.1%), 64 mg (-33.1%) \( P < 0.0001 \).
- 128 mg (-45.7%).
- BP no different across 3 treatment groups.
- Elevated serum potassium levels (K+ > 5.5 mEq/L) led to withdrawal of 11 patients.

What Next

• Despite adequate BP control.

• Proteinuria continues
Frusemide 80mg

What Next

• Despite adequate BP control.

• Proteinuria continues
Spironolactone

Overall further reduction UAER 30%.

Type 2-Rossing et al. Diabetes Care. 2005;28:2106-12
Type 1 + Type 2 Schjoedt et al. Kidney Int June 2006; 1-7
Anti-albuminuric effect of the aldosterone blocker eplerenone in non-diabetic hypertensive patients with albuminuria: a double-blind, randomised, placebo-controlled trial

Ando et al. Lancet Diabetes Endocrinol 2014;2: 944-53
What Next

• Despite adequate BP control.

• Proteinuria continues
**VITAL study**

**Change in UACR** from baseline to the last measurement during treatment

- Placebo
- Combined paricalcitol
- 1 µg paricalcitol
- 2 µg paricalcitol

*Change in systolic blood pressure during treatment and withdrawal*

- Placebo
- 1 µg paricalcitol
- 2 µg paricalcitol

**24 weeks**

**Time (weeks)**

Zeeuw, D et al., *Lancet* 2010;376:543–51
Novel Therapies
### Bardoxolone Methyl and Kidney Function in CKD with Type 2 Diabetes

**Endogenous Nrf2 activator which upregulates multiple Antioxidant/Antiinflammatory genes**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (N=57)</th>
<th>Barboxolone Methyl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25 mg (N=57)</td>
<td>75 mg (N=57)</td>
</tr>
<tr>
<td>Blood pressure — mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>130.5±13.5</td>
<td>129.5±12.6</td>
</tr>
<tr>
<td>Diastolic</td>
<td>67.3±9.0</td>
<td>68.7±8.3</td>
</tr>
<tr>
<td>Glycated hemoglobin — %</td>
<td>7.2±1.2</td>
<td>7.2±0.9</td>
</tr>
<tr>
<td><strong>Medications — no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor, ARB, or both</td>
<td>57 (100)</td>
<td>55 (96)</td>
</tr>
<tr>
<td>Statin</td>
<td>45 (79)</td>
<td>46 (81)</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>35 (61)</td>
<td>31 (54)</td>
</tr>
<tr>
<td>Diuretic agent</td>
<td>51 (89)</td>
<td>48 (84)</td>
</tr>
<tr>
<td>Antidiabetic drug</td>
<td>54 (95)</td>
<td>56 (98)</td>
</tr>
<tr>
<td><strong>Laboratory results</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated GFR — ml/min/1.73 m²</td>
<td>31.2±6.3</td>
<td>32.9±7.0</td>
</tr>
</tbody>
</table>

**Pergola et al. 2011; 365: 327-36**
Bardoxolone Methyl and Kidney Function in CKD with Type 2 Diabetes

In the placebo group, muscle spasms, which were
Thank you

JD Ward
AJM Boulton
PK Thomas
AK Sharma
S Tesfaye
A Veves
G Rayman
G Sundkvist
N Efron
M Jeziorska
J Graham

http://qatar-weill.cornell.edu
http://www.medicine.manchester.ac.uk/ena/