Assessment of Retinal Vascular Geometry in Diabetic Retinopathy and its Predictive value in Disease Progression

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Diabetic Retinopathy – What we Know

• International Diabetes Federation: 246 million NOW.

• 35% of diabetics suffer with DR (93 million)
• 28 million with vision-threatening DR
• 7% with PDR (17 million)

• 3 identifiable risk factors: ↑ Glucose, ↑ BP, ↑ Cholesterol
Diabetic Retinopathy – What we Know

• In UK: prevalence (4.0 – 5.8%)
  3.2 million............(10% NHS budget)

• Middle East and North African region: highest prevalence of DM (10.9%)
  Egypt
  • 42% of diabetics suffer with end-stage DR
  • 5% classified as legally blind

Diabetic Retinopathy – What we Know

• Natural History of DM and its complications
• Features and classification of DR
• Prediction models for PDR

  - DRS
  - DRV5
  - ETDRS
  - DCCT
  - UKPDS, WESDR......and lots more
Diabetic Retinopathy
Unresolved problems

In patients with severe NPDR
  - 52% risk of developing PDR
  - 60% risk of developing high-risk PDR in 5 years

• Mismatch between severity of NPDR & retinal ischaemia
  (Featureless retina)

• “Present strategies deal with end-organ response and do not capture early disease”
• “We address established products of damaged retinal vessels”
DR- Background Research

- Digital imaging technology and vascular analysis
- Quantitative assessment of retinal vascular calibre changes.
DR- Background Research

Vascular changes with
• Development of Diabetes
• Development of DR
• Progression of DR

Recent Research

• Recent interest in assessment of further architectural and geometrical changes in the retinal vascular network

• Altered RVG
  Age
  Low birth weight
  peripheral vascular disease
  Hypertension
  Incident IHD & Stroke
  Cognitive disturbances
Purpose of the Study

• To evaluate RVG changes’ associations with increased severity of Diabetic Retinopathy

• Assess the predictive value of RVG changes as novel marker in identifying future progression to PDR

Retinal Vascular Geometry

Retinal geometrical features

• Absolute and Relative width measurements $d_0, d_1, d_2$
• Bifurcating angles $\theta, \theta_1, \theta_2$
• Area ratios and asymmetry ratios
  - Area ratio ($\beta$)
  - Junction exponent ($x$)
  - Asymmetry ratio ($\alpha$)
Retinal Vascular Geometry

- Development of custom-designed computer-assisted semi-manual rectangle technique.

Manual measurement of retinal bifurcation features.
Al-Diri B, Hunter A, Steel D, Habib M.
Diabetic Cross-sectional Study

Diabetic groups: (EURODIAB IDDM complication study)

- No retinopathy
- Minimal NPDR
- Severe NPDR
- Proliferative retinopathy

- No statistical difference in demographic and clinical data
- A total of >1500 bifurcations analysed

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Diabetic Cross-sectional Study

Results

Table 2 The distribution of geometrical measurements in the diabetic subgroups

<table>
<thead>
<tr>
<th>Retinal parameter</th>
<th>Overall data</th>
<th>No retinopathy group</th>
<th>Mild NPDR group</th>
<th>Severe NPDR group</th>
<th>PDR group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± (STD)</td>
<td>(242 bifurcations)</td>
<td>(310 bifurcations)</td>
<td>(372 bifurcations)</td>
<td>(594 bifurcations)</td>
<td></td>
</tr>
<tr>
<td>Parent Vessel Diameter $d_0$ (pixels)</td>
<td>6.97 ± (1.61)*</td>
<td>8.39 ± (2.37)*</td>
<td>8.56 ± (2.30)*</td>
<td>8.98 ± (2.63)*</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Large Child Diameter $d_1$ (pixels)</td>
<td>6.17 ± (1.56)*</td>
<td>7.44 ± (2.30)*</td>
<td>7.56 ± (2.34)*</td>
<td>8.01 ± (2.53)*</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Smaller Child Diameter $d_2$ (pixels)</td>
<td>4.96 ± (1.04)*</td>
<td>5.47 ± (1.59)*</td>
<td>5.51 ± (1.44)*</td>
<td>5.76 ± (1.70)*</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Bifurcating Angle $\beta$ (Degrees)</td>
<td>77.04 ± (15.66)*</td>
<td>79.85 ± (17.40)*</td>
<td>80.02 ± (17.81)*</td>
<td>83.23 ± (18.98)*</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Branching Angle $\alpha_1$ (Degrees)</td>
<td>25.14 ± (14.18)*</td>
<td>25.12 ± (15.08)</td>
<td>25.62 ± (15.2)</td>
<td>25.05 ± (16.7)</td>
<td>0.941</td>
<td></td>
</tr>
<tr>
<td>Branching Angle $\alpha_2$ (Degrees)</td>
<td>51.97 ± (19.33)*</td>
<td>55.01 ± (21.29)*</td>
<td>54.84 ± (21.74)*</td>
<td>58.57 ± (23.73)*</td>
<td>0.027</td>
<td></td>
</tr>
<tr>
<td>Junction Exponent $\gamma$</td>
<td>3.33 ± (3.34)*</td>
<td>3.64 ± (3.17)*</td>
<td>3.20 ± (3.13)*</td>
<td>3.55 ± (3.25)*</td>
<td>0.050</td>
<td></td>
</tr>
</tbody>
</table>

The p-value of ANOVA test is shown with the significant differences between the subgroups as determined by the LSD test. (Means that do not share a symbol are significantly different.)
### Diabetic Cross-sectional Study

**Results**

- Advancing in severity of DR grade is associated with a gradual and steady increase in:
  - Vascular width of all vascular segments
  - Widening of bifurcating angle $\theta$
  - Widening of branching angle $\theta_2$
  - No change in branching angle $\theta_1$

### Table 3: The distribution of the arteriolar and venular geometrical measurements in the diabetic subgroups

<table>
<thead>
<tr>
<th>Retinal parameter</th>
<th>No retinopathy group (117 bifurcations)</th>
<th>Mild NPDR group (136 bifurcations)</th>
<th>Severe NPDR group (139 bifurcations)</th>
<th>PDR group (231 bifurcations)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artiolar data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent Vessel Diameter $d_p$ (pixels)</td>
<td>6.47 ± (1.08)*</td>
<td>7.54 ± (1.68)*</td>
<td>7.58 ± (1.65)*</td>
<td>8.06 ± (1.84)*</td>
<td>0.000</td>
</tr>
<tr>
<td>Large Child Diameter $d_L$ (pixels)</td>
<td>5.78 ± (1.12)*</td>
<td>6.65 ± (1.62)*</td>
<td>6.75 ± (1.66)*</td>
<td>7.23 ± (1.89)*</td>
<td>0.000</td>
</tr>
<tr>
<td>Smaller Child Diameter $d_S$ (pixels)</td>
<td>4.60 ± (0.90)*</td>
<td>5.42 ± (1.37)*</td>
<td>5.41 ± (1.35)*</td>
<td>5.62 ± (1.43)*</td>
<td>0.000</td>
</tr>
<tr>
<td>Bifurcating Angle $\theta$ (Degrees)</td>
<td>76.13 ± (15.8)*</td>
<td>79.14 ± (17.9)*</td>
<td>78.78 ± (18.4)*</td>
<td>84.33 ± (18.6)*</td>
<td>0.000</td>
</tr>
<tr>
<td>Branching Angle $\theta_1$ (Degrees)</td>
<td>25.77 ± (15.2)</td>
<td>27.32 ± (16.6)</td>
<td>28.33 ± (15.4)</td>
<td>27.44 ± (16.4)</td>
<td>0.560</td>
</tr>
<tr>
<td>Branching Angle $\theta_2$ (Degrees)</td>
<td>50.36 ± (20.3)*</td>
<td>51.99 ± (21.3)*</td>
<td>50.45 ± (20.3)*</td>
<td>56.88 ± (22.9)*</td>
<td>0.014</td>
</tr>
<tr>
<td>Junction Exponent $\gamma$</td>
<td>2.70 ± (1.27)</td>
<td>3.30 ± (2.00)</td>
<td>3.92 ± (1.85)</td>
<td>4.15 ± (2.25)</td>
<td>0.161</td>
</tr>
</tbody>
</table>

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**Vascular data**

<table>
<thead>
<tr>
<th>Retinal parameter</th>
<th>No retinopathy group (112 bifurcations)</th>
<th>Mild NPDR group (174 bifurcations)</th>
<th>Severe NPDR group (233 bifurcations)</th>
<th>PDR group (363 bifurcations)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent Vessel Diameter $d_p$ (pixels)</td>
<td>7.40 ± (1.87)*</td>
<td>9.94 ± (2.62)*</td>
<td>9.13 ± (2.56)*</td>
<td>6.65 ± (3.88)*</td>
<td>0.000</td>
</tr>
<tr>
<td>Large Child Diameter $d_L$ (pixels)</td>
<td>6.51 ± (1.83)*</td>
<td>8.04 ± (2.55)*</td>
<td>8.05 ± (2.54)*</td>
<td>8.50 ± (2.79)*</td>
<td>0.000</td>
</tr>
<tr>
<td>Smaller Child Diameter $d_S$ (pixels)</td>
<td>4.72 ± (1.68)*</td>
<td>5.51 ± (1.64)*</td>
<td>5.55 ± (1.47)*</td>
<td>5.82 ± (1.85)*</td>
<td>0.000</td>
</tr>
<tr>
<td>Bifurcating Angle $\theta$ (Degrees)</td>
<td>77.68 ± (15.1)</td>
<td>80.40 ± (16.9)</td>
<td>80.75 ± (17.4)</td>
<td>82.53 ± (19.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Branching Angle $\theta_1$ (Degrees)</td>
<td>24.81 ± (12.9)</td>
<td>23.43 ± (14.9)</td>
<td>24.34 ± (15.0)</td>
<td>23.53 ± (16.8)</td>
<td>0.021</td>
</tr>
<tr>
<td>Branching Angle $\theta_2$ (Degrees)</td>
<td>53.00 ± (17.9)</td>
<td>57.34 ± (20.8)</td>
<td>57.43 ± (22.1)</td>
<td>59.65 ± (23.7)</td>
<td>0.504</td>
</tr>
<tr>
<td>Junction Exponent $\gamma$</td>
<td>2.02 ± (0.26)</td>
<td>2.99 ± (0.88)</td>
<td>2.94 ± (0.89)</td>
<td>3.18 ± (1.46)</td>
<td>0.07</td>
</tr>
</tbody>
</table>
Diabetic Cross-sectional Study

• Can we detect this on **INDIVIDUAL** level

• 2 Logistic regression models
  – Patients with NO Retinopathy  VERSUS  with Retinopathy
  – Patients with NPDR  VERSUS  patients with PDR

• Using:
  Mean Parent vessel Diameter + Mean deflection of small angle

Diabetic Cross-sectional Study

• **Model 1**  [ No Retinopathy vs Retinopathy]
  – 97.6% Sensitivity and 90% Specificity

• **Model 2**  [ NPDR vs PDR]
  – 63.2% Sensitivity and 72.3% Specificity
Diabetic Longitudinal Study

- Can we **Predict Progression** to PDR in the future

<table>
<thead>
<tr>
<th></th>
<th>Non-progressors (5)</th>
<th>Progressors (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline screening visit Images</td>
<td>No DR</td>
<td>No DR</td>
</tr>
<tr>
<td>Penultimate screening visit Images</td>
<td>No DR</td>
<td>No DR</td>
</tr>
<tr>
<td>Final screening visit Images</td>
<td>No DR</td>
<td>PDR</td>
</tr>
</tbody>
</table>
Diabetic Longitudinal Study

Non-progressors (5)  Progressors (5)

Baseline Screening visit Images
No DR  No DR

Penultimate screening visit Images
No DR  No DR

Final screening visit Images
No DR  PDR

Diabetic Longitudinal Study

<table>
<thead>
<tr>
<th>Retinal parameter</th>
<th>Baseline visit (No retinopathy)</th>
<th>Penultimate visit (No or minimal NPDR)</th>
<th>Final visit (PDR)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Branching Angle $\theta_1$ (Degrees)</td>
<td>26.47 ± (14.9)</td>
<td>28.49 ± (15.3)</td>
<td>26.26 ± (13.9)</td>
<td>0.501</td>
</tr>
<tr>
<td>Branching Angle $\theta_2$ (Degrees)</td>
<td>51.28 ± (20.5)</td>
<td>49.98 ± (21.0)</td>
<td>54.07 ± (17.8)</td>
<td>0.334</td>
</tr>
<tr>
<td>Junction Exponent $\gamma$</td>
<td>3.102 ± (1.03)</td>
<td>3.01 ± (0.83)</td>
<td>3.104 ± (1.00)</td>
<td>0.721</td>
</tr>
</tbody>
</table>

Means and Standard deviations for the geometrical features in the progressors group baseline, penultimate and final visits for the overall data. P value for ANOVA test is shown.
Diabetic Longitudinal Study

Non-progressors (5) Progressors (5)

Baseline screening visit images
No DR → No DR

Penultimate screening visit images
No DR → No DR

Final screening visit images
No DR → PDR

Diabetic Longitudinal Study

Table 6 Results of binary logistic regression analysis

<table>
<thead>
<tr>
<th>Retinal parameter</th>
<th>Coeff</th>
<th>OR (95% CI)</th>
<th>p value</th>
<th>Coeff</th>
<th>OR (95% CI)</th>
<th>p value</th>
<th>Coeff</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$d_0$</td>
<td>-0.025</td>
<td>0.97 (0.84 - 1.14)</td>
<td>0.742</td>
<td>-0.145</td>
<td>0.86 (0.64 - 1.18)</td>
<td>0.352</td>
<td>-0.021</td>
<td>0.98 (0.81 - 1.18)</td>
<td>0.831</td>
</tr>
<tr>
<td>$d_1$</td>
<td>-0.007</td>
<td>0.99 (0.94 - 1.17)</td>
<td>0.934</td>
<td>-0.178</td>
<td>0.84 (0.61 - 1.16)</td>
<td>0.279</td>
<td>0.031</td>
<td>1.03 (0.84 - 1.27)</td>
<td>0.768</td>
</tr>
<tr>
<td>$d_2$</td>
<td>-0.318</td>
<td>0.73 (0.58 - 0.92)</td>
<td>0.007</td>
<td>-0.358</td>
<td>0.70 (0.49 - 1.00)</td>
<td>0.05</td>
<td>-0.301</td>
<td>0.74 (0.55 - 1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>$\theta_1$</td>
<td>-0.001</td>
<td>1.00 (0.98 - 1.02)</td>
<td>0.844</td>
<td>-0.007</td>
<td>0.99 (0.97 - 1.02)</td>
<td>0.574</td>
<td>0.002</td>
<td>1.00 (0.98 - 1.03)</td>
<td>0.858</td>
</tr>
<tr>
<td>$\theta_2$</td>
<td>0.011</td>
<td>1.01 (1.00 - 1.02)</td>
<td>0.154</td>
<td>0.014</td>
<td>1.01 (1.00 - 1.03)</td>
<td>0.123</td>
<td>0.005</td>
<td>1.01 (1.00 - 1.03)</td>
<td>0.652</td>
</tr>
<tr>
<td>$\chi$</td>
<td>-0.118</td>
<td>0.83 (0.68 - 1.01)</td>
<td>0.069</td>
<td>-0.181</td>
<td>0.83 (0.66 - 1.00)</td>
<td>0.131</td>
<td>-0.099</td>
<td>0.90 (0.84 - 1.53)</td>
<td>0.709</td>
</tr>
</tbody>
</table>
Retinal Vascular Geometry in DR

- RVG can constitute a novel marker for progression of DR and establishment as well as prediction of PDR

At Baseline Before DR
Patients at risk can be identified

Novel bio-marker of development of PDR irrespective of other DR features

The Future

Development of fully automated Diabetic Retinopathy Screening
The Future

Development of fully automated Diabetic Retinopathy Screening

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Vice Chancellor
Lincoln University

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Lecturer of computer science and informatics
Lincoln University
"Knowledge comes from learning. Wisdom comes from living."

Anthony Douglas Williams

Thank You