Retinal vessel dilatation and elongation precedes diabetic macular oedema

Jóhannes Kári Kristinsson, María Soffia Gottfredsdóttir, Einar Stefánsson

Abstract

**Aims/background**—Retinal vessel dilatation is a well known phenomenon in diabetes. In this study, the theory of whether excessive changes in diameter and length of retinal vessels occur in the development of diabetic macular oedema was tested, supporting a hypothesis that the development of diabetic macular oedema may be linked to hydrostatic pressure changes described in Starling’s law.

**Methods**—From fundus photographs of diabetic patients attending a regular eye screening programme, the diameter and segment length of retinal vessels were measured in three retinopathy groups (12 patients each) with diabetic macular oedema (DMO), background retinopathy and no retinopathy, over a period of approximately 4 years, ending at the time of diagnosis of diabetic macular oedema in the DMO group.

**Results**—A statistically significant dilatation and elongation of retinal arterioles, venules, and their macular branches was found before the diagnosis of macular oedema in the DMO group. No significant changes were found in the other two groups.

**Conclusion**—It is suggested that Starling’s law applies to the formation of oedema in the retina as in other tissues.

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Starling’s law is the general principle describing fluid movement between intravascular and interstitial compartments in tissues. It describes the balance between hydrostatic and oncotic pressure in intravascular and tissue compartments, and how fluid flux and oedema formation depend on this balance. The law predicts that increased intravascular hydrostatic pressure in the microcirculation results in a water flux out of the circulation with oedema formation, given that the oncotic pressure is constant. Even though it is undisputed as the general principle in extracellular tissue oedema formation, this law has largely been ignored in studies on retinal oedema. Based on an earlier theory we have developed a hypothesis to explain the formation of diabetic macular oedema and its disappearance following laser photoagulation. The hypothesis is based on Starling’s law and is outlined in Figure 1. In diabetes, retinal capillary non-perfusion leads to tissue hypoxia and autoregulatory dilatation of arterioles. Arteriolar dilatation decreases the resistance to flow, lessening the decrease in pressure in the arterioles (Poiseuille’s law) with a consequent increased hydrostatic pressure in the capillaries and venules. Increased vascular hydrostatic pressure leads to increased flow of fluid from the intravascular compartment into the interstitial tissue compartment according to Starling’s law. As the hydrostatic pressure within the capillaries and venules rises, the diameter of the vessels increases according to Laplace’s law. Kylstra and associates found that an increased transmural pressure in a passive tube leads to an increase in the diameter and, also, the length of the tube, or tortuosity. Robison et al reported a simultaneous development of vessel dilatation and increase in vessel length in retinal capillaries of galactose fed rats developing diabetic-like retinopathy.

Our hypothesis predicts that during the development of diabetic macular oedema we should see dilatation and elongation of the retinal arterioles and venules involved. This study was undertaken to test this hypothesis by measuring the diameter and segment length of retinal arterioles, venules, and their macular branches before the development of diabetic macular oedema and at time of diagnosis of diabetic macular oedema. Control groups involved diabetics without retinopathy and those whose background retinopathy was relatively stable throughout the observation period.

We have previously demonstrated that retinal arterioles and macular arteriolar and venular branches constrict as diabetic macular oedema disappears following laser photocoagulation, reversing the pattern described in Figure 1.

**Materials and methods**

Since 1980, the diabetic eye clinic in Reykjavik has performed annual eye examinations and fundus photography on diabetic patients. The information on each examination and treatment procedure is recorded and kept on file. From our files we selected consecutive patients treated with argon laser for diabetic macular oedema between 1992 and 1994. We excluded those who had less than 12 months of follow up before they developed macular oedema, those who had received photocoagulation treatment for proliferative diabetic retinopathy, and those whose fundus photographs were of insufficient quality. A total of 45 diabetic patients received laser treatment for macular oedema during the period. Out of those, 12 patients developed macular oedema.
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275 subjects is a well known phenomenon,9–11 and have been measured with at least a 12 month interval. In the study, each with two fundus photographs received laser treatment previously. This left 12 patients were of insulin-dependent diabetes and nine had non-insulin-dependent diabetes and one with no retinopathy had no signs of diabetic eye disease on either photograph or on annual photographs in between. The average time interval between the initial and final photographs was 49.8 (11.4) months in the BDR group and 47.3 (11.0) months in the NDR group. The mean age of patients and duration of diabetes at the time of the second photograph, were 56.6 (12.4) years and 15.3 (5.5) years for the BDR group and 60.7 (16.0) years and 15.0 (5.5) years for the NDR group, respectively.

We compared the means of the average time interval, age of patients, and duration of diabetes between the three groups, using a one way analysis of variance (ANOVA). The difference was not statistically significant.

In all cases the diameter of temporal retinal arterioles and venules and their macular branches was measured on the initial and final photographs, as well as the segment length of the superior temporal vessels. Statistical analysis was performed with the two tailed, paired Student’s t test.

DIAMETER MEASUREMENTS
The width of the retinal vessels was measured from colour fundus photographs with projection micrometry, which has been found to be a reproducible and reliable technique.13 14 The superotemporal and inferotemporal arterioles and venules were measured 1 disc diameter from the optic disc and the macular branches of the superotemporal and inferotemporal arterioles and venules were measured 1.5–2 disc diameters temporal to the optic disc. The superior temporal branches were measured 0.5–1.5 disc diameters above the superior end of the optic disc and the inferior temporal branches 0.5–1.5 disc diameters below the inferior edge of the optic disc. The photographs were projected onto a flat white screen and the vessel diameters were measured using a digital caliper and expressed in millimetres.

The horizontal diameter of the optic disc was measured and divided into the vascular diameter measurement to correct for difference in magnification between the initial and final photographs. For each vessel measured, the
Results
In the DMO group the diameter of the retinal temporal arterioles and venules and the macular branches was significantly greater at the time of diagnosis of diabetic macular oedema when compared with the earlier photographs taken, on average, 44 months earlier (Table 1). No significant change was seen in the diameter of retinal vessels in the BDR and NDR groups. The change in diameter of the retinal vessels in the DMO group was significantly different from the NDR and BDR groups (Table 2). Comparing the BDR and NDR groups gave no statistically significant difference in the diameter changes of the retinal vessels except for the superior arteriole, where the superior arterioles in those with no retinopathy dilated significantly more than in those with background retinopathy (arteriolar branch p = 0.0022, venular branch p = 0.0019). Figure 2 shows the diameter change of a superotemporal arteriolar branch in one patient over several years before diagnosis of DMO and 2 years after laser treatment.

In the DMO group, the measured segments of the superotemporal arterioles and venules and their macular branches were significantly longer at the time of diagnosis of diabetic macular oedema compared with the initial photographs (Table 3). No significant elongation of vessel segments was seen in the BDR and NDR groups. The changes in length of the retinal vessels in the DMO group were significantly different from the NDR (arteriolar branch p = 0.0022, venular branch p = 0.0108) and BDR (arteriolar branch p < 0.0001, venular branch p = 0.0019) groups. Comparing the BDR and NDR groups showed no statistically significant difference in the length changes of the retinal vessels.

Discussion
The data fail to disprove the hypothesis outlined in Figure 1. A statistically significant dilatation and elongation of superotemporal and inferotemporal arterioles and venules and their branches precede the formation of DMO.

Table 1 Change in diameter in the groups: initial diameter/final diameter. Mean, standard deviation (SD), and the p value (where this is below 0.05) is given using a paired two tailed Student’s t test (n=12).

<table>
<thead>
<tr>
<th>Group</th>
<th>Diameter Change</th>
<th>Average</th>
<th>SD</th>
<th>p Value</th>
<th>Average</th>
<th>SD</th>
<th>p Value</th>
<th>Average</th>
<th>SD</th>
<th>p Value</th>
</tr>
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<tr>
<td>DMO</td>
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<td>0.2765</td>
<td>0.0362</td>
<td>0.0001</td>
<td>1.0425</td>
<td>0.0688</td>
<td>NS</td>
<td>0.9773</td>
<td>0.0586</td>
<td>NS</td>
</tr>
<tr>
<td>BDR</td>
<td>Inferotemporal arteriole</td>
<td>0.1346</td>
<td>0.0163</td>
<td>0.0001</td>
<td>1.0425</td>
<td>0.0688</td>
<td>NS</td>
<td>0.9773</td>
<td>0.0586</td>
<td>NS</td>
</tr>
<tr>
<td>NDR</td>
<td>Superotemporal arteriolar branch</td>
<td>0.1939</td>
<td>0.0226</td>
<td>0.0001</td>
<td>1.0425</td>
<td>0.0688</td>
<td>NS</td>
<td>0.9773</td>
<td>0.0586</td>
<td>NS</td>
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<td></td>
<td>Inferotemporal arteriolar branch</td>
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<td>0.9773</td>
<td>0.0586</td>
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<tr>
<td></td>
<td>Superotemporal venule</td>
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<td>0.0141</td>
<td>0.0001</td>
<td>1.0425</td>
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<td>0.0090</td>
<td>0.0001</td>
<td>1.0425</td>
<td>0.0688</td>
<td>NS</td>
<td>0.9773</td>
<td>0.0586</td>
<td>NS</td>
</tr>
</tbody>
</table>

BDR = background diabetic retinopathy; DMO = diabetic macular oedema; NDR = no diabetic retinopathy.
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Venous hydrostatic pressure:

Starling’s law states that if the vascular transmural difference in hydrostatic pressure is greater than the oncotic pressure difference between the interstitial matter and blood, oedema will form:

\[ \Delta P - \Delta Q = 0 \]  

where \( \Delta P \) is the vascular transmural difference in hydrostatic pressure, and \( \Delta Q \) the oncotic pressure difference between the interstitial matter and blood. If hydrostatic pressure in the vascular compartment rises relative to the tissue pressure, this will increase the rate of fluid movement from the vessel into the tissue and form oedema if the oncotic pressure gradient remains constant. Conversely, decreased hydrostatic pressure in the vessels will pull fluid back into the vascular compartment and decrease oedema if the oncotic pressure stays unchanged.

The increased hydrostatic pressure will also dilate capillaries and venules according to Laplace’s law:

\[ T = \Delta P \frac{r}{e} \]  

where \( T \) is the wall tension of the vessel, \( \Delta P \) constitutes the transmural pressure difference, \( r \) is the vessel radius, and \( e \) relates to the wall thickness and elasticity.

In a previous report we documented a significant constriction of the same vessels following macular grid photoocoagulation for DMO. These vessels serve the macular region, where the oedema formation takes place and laser photoocoagulation is applied. Our findings strongly suggest that the pattern depicted in Figure 2 is typical for vessel changes before and after treatment for DMO. Laser photoocoagulation of the macula creates an oxygen flux from the choroid to the inner retina and the improved oxygenation will lead to an autoregulatory constriction of the arterioles which will reverse the mechanism outlined in Figure 1.

Diameter

Oxygen is a major factor in regulating retinal vessel diameter. Arterioles dilate when oxygen tension falls, for example when retinal capillaries become non-perfused. Grunwald et al found that in diabetic retinopathy, retinal vasculature shows a considerable regulatory response to oxygen, although somewhat less than in normal individuals. According to Poiseuille’s law, vasodilatation of arterioles causes a lessening of pressure decrease in the arterioles, which results in increased capillary and venous hydrostatic pressure:

\[ \Delta P = \frac{Q \eta l}{\pi r^4} \]  

where \( \Delta P \) is the pressure decrease in vessel, \( Q \) is the blood flow, \( \eta \) is the blood viscosity, \( l \) the vessel length, and \( r \) the vessel radius.

\[ T = \Delta P \frac{r}{e} \]
groups with different stages of retinopathy. We found no statistically significant change in vessel diameter in the control groups, and no change in retinal vessel diameter or segment length over an average period of 50 (BDR group) and 47 months (NDR group). Progressive average vasodilatation in diabetes may reflect dilatation in those with highly progressive retinopathy while those with less progressive disease have more constant vessel diameters. Grunwald et al reported a significantly larger average diameter of retinal venules in eyes with proliferative retinopathy and macular oedema compared with eyes with proliferative retinopathy but no oedema. Our measurements demonstrate dilatation and elongation of arterioles and venules serving the macula preceding the formation of diabetic macular oedema. No significant vessel dilatation or elongation occurred in matched diabetic controls over a similar period of time. This suggests that Starling’s law, the general law of oedema formation in the body, may participate in the pathophysiology of retinal oedema.


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