Reviewer’s report

Title: Retinal blood flow is increased in type 1 diabetes mellitus patients with advanced stages of retinopathy

Version: 0 Date: 25 Jan 2016

Reviewer: Yannis Paulus

Reviewer's report:

General comments:

The authors report a paper "Retinal blood flow is increased in type 1 diabetes mellitus patients with advanced stages of retinopathy" where they evaluate retinal capillary blood flow in the nasal and temporal region adjacent to the optic nerve. They perform this evaluation on 33 T1DM patients with proliferative DRP treated with PRP, 11 T1DM patients with npDRP, 32 T1DM patients without DRP, and 44 non-diabetic gender-matched controls along with 8 patients with DM who recently underwent PRP, both type 1 and 2. They perform scanning laser Doppler flowmetry using the Heidelberg HRF system and remove laser spots and the large vessels.

The authors thus intentionally exclude the majority of blood that supplies oxygen to the retina, namely the choroid and choriocapillaris, and also excludes the large vessels. They are analyzing capillary flow in a very limited region that is posterior. This is unlikely to represent what is happening in the retinal periphery where there is nonperfusion and laser spots. Thus, the analysis seems like it has very little significance on providing any real information that is important for disease pathogenesis.

As the authors state in their conclusion, the likely reason for all of this is "Blood from larger vessels then enters a damaged microcirculation with a diminished number of capillaries." What would be more interesting is to determine the total blood flow to the eye. Based on this limited data, it cannot be extrapolated the total blood flow to the eye or anywhere outside of this narrow region. The posterior pole and retinal periphery likely have much different stories, and there is likely a significant decrease in the periphery. The authors thus must severely limit their conclusions to only draw discussions on this small region, making it clinically much less useful.
It also means that they cannot make the conclusion that this is due to "failing vascular autoregulation in advanced diabetic retinopathy" and instead it is simply fluid mechanics due to an altered number of capillaries and their method of measurement using a limited ocular region.

Specific comments:

1. The controls provide an unfair comparison. They are "45 gender-matched healthy controls", but they are not age-matched and the authors exclude from their controls patients with Hypertension and those using statins, so patients with hyperlipidemia. Thus, they are selecting for patients without cardiovascular risk factors who are likely significantly more healthy from a CV perspective than the diabetic patients. They find this and state "Groups differed with regard to age, diabetes duration, systolic blood pressure, HbA1c and hypertension" group with proliferative DRP was significantly older than the group without DRP and controls, had higher systolic blood pressure relative to the patients without DRP and control subjects and had longer disease duration than the group without DRP (all \( P < 0.05 \))."

2. The study corrects for blood sugar levels and ensure it is between 4 and 15 mmol/l, and then reports there as no difference in the acute sugar values. Since the HbA1c values are different, likely the sugars were different. But they likely alter this value in their intervention

3. Do the authors evaluate for any medications that could cause vasodilation, such as niacin?

4. It would be helpful to evaluate the large vessels along with the choroidal/choriocapillaris circulation.

5. "Large vessels and photocoagulation scars were manually excluded, leaving only capillaries to be analyzed." We know that there is capillary drop-out and peripheral nonperfusion with DM. Since we are not assessing the entire eye but only a small region, could there not be an increase in this region and a decrease adjacent to this? Doesn't this call the entire analysis into question?
6. With PRP, the authors evaluate a heterogeneous group of 8 patients with both type 1 and 2 DM and find about the same with 2 going up slightly, 2 going down slightly, and 4 staying around the same, so no overall difference. However, they have highly variable follow-up, ranging from 2 to 12 months. This would be better to standardize this time.

**Are the methods appropriate and well described?**

If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**

If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**

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No

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