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Diabetic retinopathy-through the eyes of a diabetologist

Hans-Peter Hammes

Professor of Internal Medicine and Endocrinology, Section of Endocrinology, Fifth Medical Dept, Medical Faculty Mannheim, Heidelberg University, Mannheim, German

Clincally, diabetic retinopathy (DRP) starts with the loss of capillary cells and subsequent occlusion of capillaries, first in the deep capillary layer, then extending to the other capillary layers and secondary abortive angiogenic response by the remaining capillaries which start forming microaneurysms. With progressive disease duration, increased vascular permeability and intraretinal angiogenesis ensue. The former leads to intraretinal fluid deposition and around the fovea to diabetic macular edema, while the latter, when the new vessels penetrate the inner limiting membrane, form proliferative retinopathy. Disease staging considers only vascular pathology while pathological changes are found in all cells of the neurovascular unit of the retina. Risk factors of the DRP development are: disease duration, glycemic levels, blood pressure, and type of diabetes (T1>T2). Older obese T2D patients have a 10% increased risk of any retinopathy, and albuminuria increases the risk of any retinopathy in T2D by 16%. Underlining the role of diabetic kidney disease in the complex pathogenesis of DRP, T2 persons with macroalbuminuria have a 2.8 fold increased risk of DME, a fact that is underestimated when DRP is not considered a complication of a systemic disease. Beyond the importance of regular screening during symptom-free early stages for the prevention of sight-threatening DRP, the detection of retinal lesions indicates a more than two-fold increased risk for future CVD events in both, T1 and T2 diabetes. Regular screening for retinopathy is therefore an important tool for CVD prediction.

Recent population based studies revealed that more than 7.5% of persons studied had diabetes of which more than one fourth were previously unknown. More than 20% of persons with diabetes had retinopathy, of which 5% had vision-threatening stages. This indicates that awereness of the disease and its complications is still insufficient.

Structural retinopathy including microaneurysms, exsudates, and hemorrhages is likely preceded by endothelial dysfunction of retinal vessels. Changes in the ratio between retinal arterioles and venoles – termed arterio-venous-ration (AVR) – and flickerlight-induced vasodilation are sensitive to metabolic and hemodynamic changes preceding overt diabetes. Studying a group of patients with

morbid obesity (WHO grade III), structural retinopathy was present in 3.4% of patients. Systolic blood pressure, increased intima-media thickness of the carotid artery and impaired venolar response to flicker-light were significant predictors of the development of structural retinopathy. Since mortality can also be predicted by impaired retinal vessel dilatation, it appears that retinal vessel dysfunction is a robust biomarker of CVD and mortality.

DRP is diagnosed by vascular changes, but diabetes strikes every cell of the neurovascular unit. Attempts to improve the prediction of vision-threatening stages by measure of retinal neuronal function have failed so far, but it needs to be noted that in some patients, diabetes induced cell damage can be measured first in retinal neurons, and then in the vasculature. This corresponds to the finding that simple clinical phenotyping identifies five subtypes of T2D, which were previously lumped together. Even more important, these phenotypes differ in their propensity to develop microvascular damage, the kidney being associated with subtypes of insulin resistance, while retinopathy is linked to the level of glycemia. That glycemia is a strong effector of retinal disease is further underlined by data showing that rapid euglycemic re-entry introduced by GLP-1 receptor agonists can sometimes deteriorate retinopathy. As the retina does not express the GLP-1 receptor to a great extent, and even looses the minimal expression in some ganglion cells during DRP progression, this effect is the consequence of systemic factors, not copied by other novel drugs such as SGLT-2 inhibitors or DPP4 inhibitors. The risk of euglycemic re-entry in T2D is almost exclusively explained by pre-existing retinopathy.

Therefore, diabetologists should use the eye as a window to the body's vasculature, and use fundus screening as a personalized biomarker of disease progression and general CVD risk.