The Eye as an Indicator of Heart Failure in Diabetic Patients*

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In 1855, Eduard Jaeger, an Austrian physician, was the first to painstakingly portray the retinal findings associated with diabetes in his seminal work “Beiträge zur Pathologie des Auges” (1). With a newly developed direct ophthalmoscope, he produced one of the first atlases containing 21 color plates of fundus paintings and described a “roundish” or oval yellowish spots and full or partial thickness extravasations through the retina in the macular region of a diabetic patient (1). Jaeger findings of the association between diabetes and retinal changes were controversial and were not adopted by the medical community. The debate as to whether macular changes were directly related to diabetes or whether they were caused by atherosclerosis and hypertension was unresolved at the beginning of the 20th century, until Arthur James Ballantyne, suggested that diabetic retinopathy represents a unique form of vasculopathy and his work showed for the first time the role of capillary wall alterations in the development of diabetic retinopathy as well as the presence of deep waxy exudates in the outer plexiform layer (2).

More than 150 years after the original description, researchers have correlated diabetic retinopathy with a disease that Jaeger and others probably did not encounter too often: heart failure (HF).

Heart failure is today a common cause of morbidity and mortality worldwide. In the U.S. alone, HF occurs in more than 5 million people and it accounts for more than 1 million hospital stays. In addition, $33 billion in health care costs annually are spent on patients with HF (3).

Research on the etiology of HF has focused on diseases that have traditionally been thought to reflect macrovascular damage, such as hypertension (HTN), myocardial infarction, diabetes, and renal dysfunction (4,5). There has not been much focus on microvascular disease as a harbinger of HF.

Although several studies have linked microvascular damage to the development of coronary heart disease (CHD) (6–14), Wong et al. (15) were the first to show with a large population-based database that retinopathy is an independent predictor of congestive HF. With the ARIC (Atherosclerosis Risk in Communities) study (a prospective cohort study of atherosclerosis risk factors in 4 U.S. communities), they studied the relationship between retinopathy and new-onset HF. In 11,612 healthy middle-aged participants, they found an almost 2-fold-higher risk of HF for those patients with retinopathy after controlling for common CHD risk factors such as age and blood pressure. Most interestingly, further analysis revealed that in diabetic patients without history of CHD or HTN, the presence of retinopathy conferred a 4-fold increase in risk of HF (risk ratio of 4.32 with 95% confidence interval 2.13 to 9.76). In addition the population-attributable fraction of retinopathy in the diabetic patient without CHD or HTN was an astounding 30.5%, implying that microvascular disease might play a significant role in the pathophysiology of HF in diabetes. However, this subgroup analysis was restricted by a significant number of unaccounted confounders (e.g., renal dysfunction and glycemic control) (15).

In this issue of the Journal, Cheung et al. (16) elegantly expand on their prior work to describe the relationship between diabetic retinopathy and the development of HF while controlling for several of the confounders in their original study. Again with the ARIC database, they followed 1,021 diabetic patients with normal renal function and no evidence of coronary disease or HF for 9 years. The authors found that, in this group of otherwise healthy diabetic patients, those with baseline retinopathy were more than twice as likely to develop HF as patients without retinopathy at baseline. This increased risk persisted after controlling for common HF risk factors including age, gender, smoking history, blood pressure, lipid profile, and other risk factors such as race, diabetes duration, and insulin use (hazard rate 2.71). Further adjustments for glycemic control, carotid atherosclerosis, and markers of endothelial dysfunction did not change the results significantly (hazard rate 2.20). Almost 1 in 4 (this changes to 1 in 5) diabetic patients with baseline retinopathy developed HF (cumulative incidence of 21.6%), whereas only 1 in 10 (1 in 12) patients without baseline retinopathy developed HF (cumulative incidence of 8.5%). Even mild retinopathy (defined as minimal, nonproliferative retinopathy) conferred an increased risk with a hazard rate of 1.91, whereas moderate-severe retinopathy (defined as moderate-severe nonproliferative retinopathy or proliferative retinopathy) conferred a higher risk with a hazard rate of 2.38 (16).

There are some limitations to the conclusions we can draw from this study. As the authors note, some of the

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biochemical markers (e.g., glycosylated hemoglobin) were obtained, on average, 3 years before the bulk of the data. Another weakness is the fact that only white and black Americans were included in this study, limiting its applicability to other races. Lastly, a considerable number of the diabetic patients had sub-par retinal photographs and were thereby excluded, introducing the possibility of selection bias. Most importantly, this study shows an association between diabetic retinopathy and HF but certainly does not prove causality.

The mechanism by which microvascular disease as manifested by retinopathy might play a role in the pathophysiology of HF in diabetes remains to be elucidated. Retinopathy has been associated with inflammatory markers and measures of endothelial dysfunction such as C-reactive protein and serum soluble intercellular adhesion molecule-1 (17,18). It is possible that retinopathy is an early sign of inflammation and endothelial dysfunction that eventually leads to coronary microvascular disease and HF. Another explanation is that retinopathy simply lies along a continuum of disease that eventually leads to macrovascular damage and HF. Clarifying the relative contribution of micro- and macrovascular damage to HF in diabetic patients is vital from etiological, preventive, and therapeutic perspectives.

In summary, this is the first large prospective population-based study finding that in the diabetic patient the presence of retinopathy confers an increased risk for developing HF even in the absence of conventional risk factors. For the physician, this finding might have important clinical implications in the care of diabetic patients. The current guidelines already identify the need for routine screening for retinopathy in the diabetic patient. In addition to appropriate vision care, the detection of retinopathy might now also warrant a fuller cardiac evaluation and closer follow-up to prevent the development of HF.

Sixteen hundred years ago Saint Jerome said “. . . eyes without speaking confess the secrets of the heart” (19). Never was this truer than when examining the relationship between retinopathy and HF in diabetes.

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