EDITORIAL (SEE ZAVRELOVA ET AL., P. 867)

Diabetic Retinopathy in 2011: Further Insights From New Epidemiological Studies and Clinical Trials

Diabetic retinopathy (DR) is a common and specific microvascular complication of diabetes and one of the leading global causes of preventable blindness. Population-based studies suggest that about one-third of the diabetic population have signs of DR and approximately one-tenth have vision-threatening stages of retinopathy, such as diabetic macular edema and proliferative retinopathy (1,2). Notwithstanding its effects on vision, DR is costly (3), substantially impacts on the patient's quality of life (4), and is linked with a greater risk of life-threatening systemic vascular complications (5).

Because blindness from DR is preventable from both public health screening and clinical management perspectives, it is important to precisely identify persons at risk for developing DR and those most likely to progress to severe vision-threatening stages. In this issue of *Diabetes Care*, Zavrelova et al. (6) present a fascinating and informative article that discusses people with diabetes having distinct developmental patterns of DR and that there may be specific risk factors associated with different patterns of progression. From a large group of patients with type 2 diabetes ($N = 3,343$), the authors identified five clusters of developmental patterns of DR. The largest (cluster A) included patients who did not develop any form of DR over a 6-year period ("persistent no retinopathy"). Cluster B included patients with a high probability of a mild form of DR, which disappeared over time and thus are not at risk for vision loss. Two progressive clusters (C and D) were identified and differed from each other in severity and in speed of developing retinopathy. Finally, a fifth cluster (E) consisted of patients who had persistent proliferative DR, including previous laser treatment.

Perhaps the most important finding was that almost 90% of this population (cluster A) were considered to have "persistent no retinopathy" after 6 years. Furthermore, there was another 4.9% of people (cluster B) with mild DR and signs of a "slow regression" of retinopathy over time. Thus, in total, nearly 94% of people with type 2 diabetes are not at risk for developing vision-threatening retinopathy. Contemporary population-based longitudinal data for DR are scarce although prospective data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) in the U.S. have shown a reduction in the annualized incidence and progression of DR in type 1 patients in recent years (7,8). Thus, the phenomenon observed in the study by Zavrelova et al. is supported by WESDR data and could reflect effective screening and improvements in the control of systemic risk factors in diabetes care in the last two decades (9–12). Further work is clearly needed to establish whether diabetes care is indeed having a positive and sustained influence on diabetes complications as it would reinforce the impact and effectiveness of substantial public health efforts in tackling diabetes around the world.

Glycemic control remains the foundation for diabetes care. Consistent with landmark studies such as the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS), which have provided strong evidence of the benefits of good glycemic control in reducing the risk of development and progression of DR in both type 1 and type 2 diabetes (13,14), Zavrelova et al. report that patients in the two nonprogressive clusters had lower mean values of HbA_{1c} than patients in the progressive clusters C, D, and E over time. These findings also support recent data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye trial, which found a significant difference in three-step progression of DR between those with intense glycemic control compared with those with standard care (15).

Interestingly, total cholesterol was also consistently lower in the nonprogressive group (clusters A and B) compared with the progressive groups (clusters C and D) suggesting a role of lipids in the developmental patterns of DR. Previous studies have reported dyslipidemia as a factor in the pathogenesis of DR, but major clinical trials showing the effect of lipid lowering on DR progression have not been conclusive (16). In the last 3 years, however, two major randomized trials, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and the ACCORD Eye trials, have firmly demonstrated that fenofibrate may play an important role in decreasing the progression of DR. The ACCORD Eye trial, which compared fenofibrate with placebo in patients on statins, confirmed the superiority of fenofibrate in preventing the progression of DR with a risk reduction similar to that of FIELD (30–40%) (17). However, because this effect was not associated with a significant reduction in serum cholesterol levels, further studies are needed to better understand the mechanisms underpinning the effect of fenofibrate (17). There are suggestions that fenofibrate may have effects on nonlipid pathways such as inflammation, endothelial function, and vascular endothelial growth factor (18).

Zavrelova et al. also confirm the importance of blood pressure control on the developmental patterns of DR in this sample. In their article, systolic blood pressure (sBP) control appears to play a more important role than diastolic blood pressure, with the two progressive clusters (C and D) correlated with periods of deterioration in sBP ranging between 10–15 mmHg in these two groups. In contrast, at no time during the follow-up was there an increase in sBP exceeding 5 mmHg in clusters A and B. These findings indicate that large increments in sBP may impact on the progression of DR in type 2 patients, and they confirm previous reports that for each 10-mmHg increase in sBP, there is an approximately 10% excess risk of early DR and a 15% excess risk of proliferative retinopathy (19,20).

Data from new clinical trials, however, suggest that there is a limit to the effectiveness of blood pressure control in preventing DR. In contrast to the UKPDS, both the Action in Diabetes and Vascular Disease (ADVANCE) study and the ACCORD Eye trial did not find intensive blood pressure control to be useful in reducing the progression of DR. This

could be related to a short follow-up time in the ACCORD Eye trial (~5 years) compared with the 20-year follow-up of the UKPDS, where tighter blood pressure control reduced the risks of retinopathy progression by about one-third, visual loss by one-half, and the need for laser treatment by one-third in people with type 2 diabetes (21,22). It is also possible that the aggressive lower blood pressure targets set by the ACCORD Eye trial, i.e., sBP <120 mmHg (compared with <150 mmHg in the UKPDS), may indicate a floor effect to the benefits of lowering blood pressure below normal ranges (17).

While the article by Zavrelova et al. (6) shows distinct developmental patterns of DR and associated specific risk factors, it has some shortcomings that future studies should focus on. The most significant one is a lack of information associated with the profile of each cluster that could lead to the optimization of treatment by targeting different patient groups. An understanding of the role of the duration of diabetes across these clusters is also lacking and needs to de further investigated. From a public health perspective, improving our understanding of who is unlikely to progress (or even likely to regress) has economic and clinical implications on differential possible screening intervals in selected patients. Such patients, for example, could be screened yearly for 2 or even 3 times. Conversely, those at higher risk of progression require more frequent monitoring. Another important area of future research is to understand whether patients can change from one cluster to another. For example, it would be interesting to investigate whether these data could be used to help patients who are likely "progressors" to improve their glucose management. Future work investigating these limitations would have significant implications and extend on the findings reported by Zavrelova et al.

In conclusion, considering the current high prevalence estimates of DR and vision-threatening DR and the anticipated tripling of the number of people worldwide to develop type 2 diabetes by 2040 (23), the finding that over 90% of that population are not at risk for developing severe DR in the short term is quite promising. A longer follow-up period (>15–20 years with regular eye examinations) for these patients is therefore warranted to ascertain if this phenomenon persists longitudinally, and what risk factors are associated with progression if it is evident; inform patients about the progression of DR in the three progressive clusters; and finally, optimize these data to better inform patients of the public health initiatives and clinical practices.

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