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Determinants of the Risk of Diabetic Kidney Disease and Diabetic Retinopathy Independent of Glucose Exposure

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The Diabetes Control and Complications Trial (DCCT) confirmed that intensive glucose control reduced the risk of diabetic mellitus retinopathy (DMR) and diabetic kidney disease (DKD) development by 76% and 34% and 44%, respectively, compared with standard treatment [1]. However, the subsequent analyses by DCCT/Epidemiology of Diabetes Interventions and Complications study group raised the issue that total glycemic exposure (glycosylated hemoglobin [HbA1c] and duration of diabetes) explains only about 11% of the variation in retinopathy risk [2]; therefore, other factors might be responsible for the remaining 89% of the variation in risk among subjects independently of HbA1c.

Glycemic variability has been suggested as an independent risk factor in diabetic microvascular complications through many epidemiological studies [3]. *In vitro* and *in vivo* studies confirmed that glycemic variability induces epigenetic changes in the promoter of nuclear factor-κB [4] and increases oxidative stress leading to cellular apoptosis [5]. Furthermore, high glycemic variability is apparently associated the risk of concurrent hypoglycemia [6]; the cellular processes that occur with hyperglycemic spikes are also induced by experimental hypoglycemia [7].

Yun et al. [8] added the evidence for the significant association between glycemic variability and DKD. They specifically showed that HbA1c variability affected the development and progression of DKD in type 2 diabetic patients with advanced DMR. Although their study did not show whether there is a difference in the degree of effect of HbA1c variability on DKD according to the presence or absence of advanced DMR, both of short term and long term glucose variability have been known to also increase the risk of DMR [9].

Yun et al. [8] also showed that lipid level was another determining factor of DKD in type 2 diabetic patients with advanced DMR; however, dyslipidemia is also known to affect the risk of DMR [10] as well as DKD [11]. In addition, fenofibrate was shown to reduce DMR progression in patients with type 2 diabetes in The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study [12] and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study [13], although triglyceride level could not explain the effect of fenofibrate.

As the authors mentioned, the discrepancy between the severity of DMR and DKD has already been reported even in one individual [14,15]. In the study of Yun et al. [8], 37.2% of patients with advanced DMR did not have any DKD; and 31.1% of patients with severe DKD did not have advanced DMR. Furthermore, in the case of DMR, there has been evidence that DMR can develop independent of glucose exposure or glucose variability: retinal microaneurysms can be detected even in individuals with normal glucose tolerance [16] or prediabetes [17].

Genetic factors might explain the susceptibility to DMR and

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DKD independently of glucose exposure. *VEGFA*, *ACE*, *AKR1B1*, *APOC1*, *APOE*, and *CCL2* have been suggested as risk genes for DKD [14,18,19]; and *VEGF*, *AKR1B1*, and *CCDC101* for DMR [15,20]. Furthermore, Kim et al. [14] compared the patients with end-stage renal disease (ESRD) due to type 2 diabetes and the patients with DMR without any DKD (as a control for DKD) and found that *SLC12A3* gene significantly increases the risk of ESRD [14], which suggested that genetic factors contribute to different susceptibility of DMR and DKD independently of glucose exposure.

Glucose variability as well as hyperglycemia plays an important role in the development of DKD and DMR. However, it cannot explain the difference in the susceptibility of microvascular complication in an individual. If we can differentiate the clinical and genetic risk factors between DMR and DKD, the management for the individuals with strong family history of DMR or DKD might be improved.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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