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COMMENTARY

The Role of Dyslipidemia Control in the Progression of Diabetic Retinopathy in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Diabetic retinopathy (DR) is a common microvascular complication of diabetes mellitus (DM) and is considered as the leading cause of visual impairment in working-aged adults worldwide. Dyslipidemia has been associated with DR, but not with progression to the proliferative form of DR, although the exact role in the pathogenesis of DR and diabetic macular edema (DME) remains controversial. As a result, a reasonable question arising is whether control of dyslipidemia may alter the course of DR. Statins do not appear to have an impact on DR progression. On the other hand, fenofibrate has been found to significantly reduce the rate of progression of DR in patients with pre-existing mild DR, although it has no impact on patient's vision nor on the prevention of DR development in patients with type 2 DM without DR. An interesting point that needs further evaluation is why patients without DR or those with severe DR appear to have no benefit from fenofibrate treatment.

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Diabetic retinopathy (DR) is a common microvascular complication of diabetes mellitus (DM) and is considered as the leading cause of visual impairment in working-aged adults worldwide. So far studies have found that duration of diabetes, degree of hyperglycemia, and hypertension are related to the progression of DR [1]. Dyslipidemia has been also associated with DR, but not with progression to the proliferative form of DR. In fact, serum lipids have been reported to be a risk factor for DR and diabetic macular edema (DME), suggesting that permeability changes in the retinal microvasculature result in extravascular accumulation of lipoprotein deposits, although the exact role in the pathogenesis of DR and DME remains controversial. Moreover, a recent meta-analysis demonstrated that total cholesterol (TC), triglycerides (TGs), and low-density lipoprotein (LDL) cholesterol were significantly higher in persons with DME compared to those with DM without DME [2]. Therefore, a reasonable question arising is whether control of dyslipidemia may alter the course of DR.

Das et al. in their meta-analysis found that there was not a significant improvement for lipid-lowering therapy compared with placebo with respect to the progression of hard exudates or severity of DME, although some of the

studies included in the meta-analysis suggested some benefit [2]. In addition, statins, which reduce LDL and are widely used for the treatment of dyslipidemia, do not appear to have an impact on DR progression [3]. On the other hand, fenofibrate has been found to be beneficial in reducing the progression of DR in patients with pre-existing retinopathy, independent of its effect on dyslipidemia control [4–6]. Specifically, fenofibrate is a peroxisome proliferator activated receptor alpha (PPARα) agonist, which reduces TGs and LDL and increases high-density lipoprotein (HDL) cholesterol. Its mechanism of action is postulated to involve lipid metabolism, endothelial function, anti-apoptosis, anti-inflammation, and anti-oxidation, while its beneficial effect on DR progression has been evaluated in two large randomized clinical trials [4–6].

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was a multicenter randomized trial, which evaluated the effect of fenofibrate 200 mg/day in about 9795 adult patients with type 2 DM [4]. The results of this study showed that the rate of first laser treatment for DR was significantly reduced in patients at the fenofibrate group compared to controls over an average of 5 years (3.4% vs. 4.9%, respectively, HR 0.69). In addition, there was a relative reduction in the need for laser treatment of 36% with fenofibrate treatment in those with any maculopathy and of 38% in those with proliferative DR [4, 5]. Of note, the effect of fenofibrate was evident 8 months after treatment with progressively greater benefits over time.

Apart from the analysis regarding the entire cohort, a substudy in 1012 patients, whose DR was graded on the basis of Early Treatment Diabetic Retinopathy Study (ETDRS) criteria, was conducted to investigate the progression of DR [5]. In this study, there was no difference in the proportion of patients with a two-step progression in DR between patients in the fenofibrate and control group (9.6% vs. 12.3%, respectively, $p = 0.19$). However, in patients with pre-existing DR, significantly fewer patients in the fenofibrate group showed a two-step progression compared to those in the placebo group (3.1% vs. 14.6%, $p = 0.009$). On the contrary, the number of patients without pre-existing DR who had a two-step progression of DR was similar in the two groups (11.4% vs. 11.7%, $p = 0.87$), while the incidence of any new DR was not different between the two groups [5]. It is also worthy to note that the FIELD study found that the benefit in the progression of DR or the reduction in the need for laser treatment was unrelated to serum lipid levels, suggesting a complex association between serum dyslipidemia and DR/DME [4, 5].

The other large randomized controlled trial evaluating the effect of the management of systemic factors (hyperglycemia, hypertension, hyperlipidemia) on the progression of DR was the Action to Control Cardiac Risk in Diabetes (ACCORD) eye study, comprising 2856 subjects with type 2 DM [6, 7]. After 4 years, the proportion of patients who presented with progression of DR of three or more steps on the ETDRS severity scale or required laser photocoagulation/vitrectomy was significantly less in patients receiving fenofibrate 160 mg/day plus statin than in those receiving statin alone (6.5% vs. 10.2%, respectively, $p = 0.006$), while there was no statistically significant difference in the rates of moderate visual loss or macular edema between the two groups [6, 7]. Furthermore, no significant difference in progression of DR was observed for those without any DR and for those with moderate or severe non-proliferative disease [6]. However, this beneficial effect of fenofibrate in reducing DR progression no longer persisted after discontinuation of treatment 4 years post ACCORD study closeout, with 11.8% of patients in the fenofibrate group and 10.2% of patients in the control group presenting with DR progression ($p = 0.60$) [7].

In any case, it should be noted that although the control of dyslipidemia is important, it has to be taken into account that there may be an interplay between various risk factors and dyslipidemia in patients with DR [8]. Blood pressure is one of the most significant factors that may interact with dyslipidemia in patients with DM, but the impact of its control on DR progression remains controversial. Esmann et al. showed that hard exudates in DR were correlated with the duration of DM, the blood pressure, and the serum cholesterol levels, suggesting that hard exudates seem to be a

characteristic sign in the slow and insidious development of DR, in which dyslipidemia and blood pressure may interact [9]. However, according to a recent meta-analysis, reduction of blood pressure could not prevent or slow DR, although treatment to reduce the blood pressure of people with DM is warranted for other health reasons [9, 10].

Taken as a whole, in both FIELD and ACCORD eye studies fenofibrate has been found to significantly reduce the rate of progression of DR in patients with pre-existing mild DR, although it has no impact on patient's vision nor on the prevention of DR development in patients with type 2 DM without DR. An interesting point that needs further evaluation is why patients without DR or those with severe DR appear to have no benefit from fenofibrate treatment. Additionally, both trials did not use optical coherence tomography (OCT) to assess DME and none had DR as a primary endpoint. Therefore, it would be of great interest to analyze the effect of fenofibrate in controlling DME using OCT, as well as to investigate its impact on the treatment of DME with anti-vascular endothelial growth factors.

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