

The role of triglycerides in the pathogenesis of microvascular complications of diabetes mellitus

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Microvascular complications of diabetes mellitus (DM) represent a major public health problem. Approximately 34%-40% of patients with DM have chronic kidney disease (albuminuria or impaired kidney function). Moreover, 3.3% of adults in US have diabetic nephropathy whereas in subjects > 65 years-old, 10.7% has diabetic nephropathy. In addition, 44% of patients undergoing dialysis in the US have DM. Importantly, patients with diabetic nephropathy have higher all-cause mortality than patients with coronary heart disease. Regarding diabetic retinopathy, it affects 27%-40% of patients with DM and is leading cause of blindness in working-aged adults. Even though the incidence of diabetic retinopathy has declined in the last decades, its prevalence increased and is expected to rise further as a result of the increasing incidence of type 2 DM and the longer life expectancy of patients with DM. Diabetic neuropathy is the most early complication of DM and the leading cause of non-traumatic amputation in high-income countries. Autonomic diabetic neuropathy is also associated with increased cardiovascular risk.

Emerging data suggest that elevated triglycerides are implicated in the pathogenesis of microvascular complications of DM. Several observational studies in patients with both type 1 and type 2 DM suggested that elevated triglyceride levels are associated with increased risk for development of albuminuria and for decline in renal function. In the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (n = 988 patients with type 1 DM) and in the Early Treatment Diabetic Retinopathy Study (n = 3.711 patients with type 2 DM), the severity of retinopathy was positively associated with triglyceride levels. In contrast, triglyceride levels do not appear to predict the progression of retinopathy in patients with type 1 DM. Moreover, several observational studies in both patients with type 1 and type 2 DM suggested that elevated triglyceride levels are associated with increased risk for development of peripheral and autonomic neuropathy.

It also appears that the reduction of triglyceride levels with fibrates prevents or delays the progression of microvascular complications of DM. In the Diabetes Atherosclerosis Intervention Study (n = 314 patients with type 2 DM), treatment with fenofibrate for 38 months reduced the worsening of albumin excretion and reduced the

incidence of new-onset microalbuminuria. In the *Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)* trial (n = 9,795 patients with type 2 DM), patients who received fenofibrate experienced an increase in serum creatinine levels by 0.11 mg/dl more than patients treated with placebo but the decline of glomerular filtration rate during the study was slower in patients treated with fenofibrate (by 0.8 ml/min/1.73m² annually compared with placebo) during a follow-up of 5 years. Fenofibrate also reduced urine albumin excretion by 14% more than placebo. In the *Action to Control Cardiovascular Risk in Type 2 Diabetes (ACCORD)* trial (n = 5,518 patients with type 2 DM), patients who received fenofibrate combined with simvastatin experienced an increase in serum creatinine levels by 0.06 mg/dl more than patients treated with simvastatin monotherapy during a follow-up of 4.7 years. On the other hand, fenofibrate reduced the incidence of both new-onset microalbuminuria and new-onset macroalbuminuria by 10%. Regarding the effects of fibrates on diabetic retinopathy, in the *FIELD* trial, treatment with fenofibrate for 5 years reduced the need for laser photocoagulation by 31% (p = 0.002) compared with placebo. Fenofibrate also reduced the risk of progression of retinopathy by 79% (p = 0.004). It was estimated that 17 patients with retinopathy had to be treated with fenofibrate for 5 years to prevent one laser treatment. However, fenofibrate had no effect on the development of retinopathy in patients without retinopathy at baseline. Moreover, fenofibrate did not prevent the deterioration of visual acuity. In the *ACCORD Eye* study (n = 2,856 patients with type 2 DM), treatment with fenofibrate for 4 years reduced the rate of progression of retinopathy by 40% (p = 0.006) compared with placebo. However, fenofibrate did not affect the occurrence of moderate vision loss. Fenofibrate is currently licensed in some countries for the management of diabetic retinopathy. Finally, regarding the effects of fibrates on diabetic neuropathy, in the *Fremantle Diabetes Study* (1,237 patients with type 2 DM), the use of fenofibrate was independently associated with 70% lower risk for prevalent peripheral neuropathy. Moreover, in the prospective cohort of the same study (531 patients with type 2 DM followed-up for 5 years), treatment with fenofibrate reduced the risk of incident peripheral neuropathy by 48%. In the *FIELD* trial, fenofibrate re-

duced the risk of first amputation by 36% and the risk of minor amputation without known large-vessel disease by 47%. However, fenofibrate had no effect on the incidence of major amputations.

It should be mentioned that the beneficial effects of fibrates on the microvascular complications of DM are not an indisputable proof that triglycerides are implicated in the pathogenesis of these complications. Indeed, fibrate increase high density lipoprotein cholesterol (HDL-C) levels and also exert antiinflammatory and antioxidant effects. These actions might also play a role in the prevention and treatment of microvascular complications of DM. Indeed, the effects of fibrates on microvascular complications appeared to be independent of changes in the lipid profile. Moreover, these benefits were apparent within 8 months of initiation of fenofibrate treatment, suggesting that other mechanisms than lipid-lowering might be implicated.

More limited data suggest that omega-3 fatty acids, which also reduce triglyceride levels, might also prevent or delay the progression of microvascular complications of DM. In a recent study in 262 patients with type 2 DM, treatment with omega-3 fatty acids for 1 year prevented the increase in albuminuria. In another recent study in 344 patients with type 2 DMI, treatment with omega-3 fatty acids for a median of 1.4 years reduced albuminuria and prevented the decline in renal function. Regarding the effects of omega-3 fatty acids on diabetic retinopathy, in an early study, administration of omega-3 fatty acids to streptozotocin-induced diabetic rats did not affect pericyte loss and increased the formation of acellular, occluded capillaries in the retina. In contrast, in more recent animal studies, treatment with omega-3 fatty acids preserved retinal function. However, there are no studies that evaluated the effects of omega-3 fatty acids on diabetic retinopathy in humans. Finally, regarding the effects of omega-3 fatty acids on diabetic neuropathy, in an early study in patients with type 2 DM, treatment with eicosapentaenoic acid for 48 weeks improved clinical symptoms (coldness, numbness) and the vibration perception threshold sense of the lower extremities. In a pilot study in 40 patients with type 1 DM, treatment with omega-3 fatty acids for 1 year increased corneal nerve fiber length but did not affect sensory function or nerve conduction. In another study in 24 patients with type 2 DM, treatment with

omega-3 fatty acids for 6 months improved autonomic neuropathy. However, these preliminary data do not necessarily mean that triglycerides are implicated in the pathogenesis of microvascular complications of DM, since omega-3 fatty acids also appear to exert antiinflammatory and antioxidant effects, which might also play a role in the amelioration of these complications.

In conclusion, epidemiological data suggest that triglycerides might be implicated in the pathogenesis of all microvascular complications of DM. Clinical studies also suggest that reduction of triglyceride levels with either fibrates or omega-3

fatty acids might prevent or improve these complications. However, other mechanisms might also be implicated in these beneficial effects of fibrates and omega-3 fatty acids. More importantly, the effects of reduction of triglyceride levels on the macrovascular complications of DM are unclear. Therefore, lowering triglycerides is not currently recommended as a part of the prevention or management of the microvascular complications of DM. Treatment with fibrates or omega-3 fatty acids is recommended only in patients who have non-HDL-C levels > 100 mg/dl despite achieving low-density lipoprotein cholesterol targets with a potent statin.