Cardiovascular journals

New treatment targets to prevent microvascular complications in type 2 diabetes

Marc Evans
Consultant Physician, Llandough Hospital, Cardiff

Microvascular complications, such as kidney disease and retinopathy, are an important consequence of diabetes, resulting in major clinical and health-economic implications. Intensive blood pressure and blood glucose control may reduce the risk of microvasculopathy; however, the achievement of optimal blood pressure and blood glucose levels is often difficult owing to treatment-limiting issues such as hypoglycaemia. It is thus important to identify other potential therapeutic targets that may be of benefit in terms of reducing the burden of microvascular disease in people with diabetes.

Epidemiological evidence implies a link between diabetic kidney disease and plasma triglyceride levels, with less consistent findings with respect to HDL-cholesterol levels and kidney disease (Retnakaran et al, 2006). In clinical trials, the use of fenofibrate has been associated with reduced decline in renal function, reduced albuminuria and reduced need for laser treatment of retinopathy (Davis et al, 2011). The precise mechanisms underlying such observations remain unclear; therefore, the objective of the international study by Sacks et al (summarised alongside) was to determine whether low HDL-cholesterol levels and elevated plasma triglycerides are associated with diabetic kidney disease and retinopathy, independent of recognised determinants of microvascular disease, in people with LDL-cholesterol levels <3.4 mmol/L.

The authors used a case–control design across 24 sites in 13 countries. The case subjects comprised 2535 people with type 2 diabetes with an average disease duration of 14 years. Overall, 1891 of these had kidney disease and 1218 had retinopathy. The case subjects were compared with 3683 control subjects with type 2 diabetes matched in terms of disease duration, age, gender and LDL-cholesterol levels but without evidence of kidney disease or retinopathy. Case–control analyses were conducted using logistic regression and multivariate models that adjusted for HbA_{1c}, hypertension and statin treatment.

The risk of microvascular disease (kidney disease or retinopathy) increased by 16% (odds ratio [OR], 1.16) for every 0.5-mmol/L increase in plasma triglyceride level, and decreased by 8% (OR, 0.92) for every 0.2-mmol/L increase in HDL-cholesterol level. For kidney disease alone, the OR was 1.23 for each 0.5-mmol/L increase in plasma triglyceride level, and 0.86 for each 0.2-mmol/L increase in HDL-cholesterol level.

While this study has various limitations, in particular its reliance on patient-level data derived from medical records and the absence of any detailed lipoprotein sub-fraction data, these results clearly demonstrate independent associations between plasma triglyceride and HDL-cholesterol levels and microvascular disease, in particular diabetic kidney disease. Current guidelines largely focus on lipid modification – particularly LDL-cholesterol reduction – with regard to macrovascular disease. With the growing prevalence of diabetic kidney disease, the data from this study support the rationale for developing additional lipid targets beyond LDL-cholesterol when considering this aspect of diabetes. ■

Davis TM, Ting R, Best JD et al (2011) Effects of fenofibrate on renal function in patients with type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study. *Diabetologia* **54**: 280–90

Retnakaran R, Cull CA, Thorne KI et al (2006) Risk factors for renal dysfunction in type 2 diabetes: U.K. Prospective Diabetes Study 74. *Diabetes* **55**: 1832–9

Circulation

Effects of plasma triglyceride and HDL-cholesterol levels on diabetic kidney disease and retinopathy

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓

1 The authors sought to determine the effects of low HDL-cholesterol and high triglyceride levels on the incidence of diabetic kidney disease and retinopathy in people with T2D and LDL-cholesterol levels ≤3.4 mmol/L.

2 They recruited 2535 people with T2D and kidney disease and/or retinopathy, and compared them with 3683 matched control subjects with T2D but no evidence of these complications.

3 The odds ratios (ORs) for any microvascular complication were found to be 1.16 (95% confidence interval [CI], 1.11–1.22) for each quintile (0.5 mmol/L) increase in triglyceride level, and 0.92 (95% CI, 0.88–0.96) for each quintile (0.2 mmol/L) increase in HD-cholesterol level.

4 The ORs for kidney disease alone were 1.23 (95% CI, 1.16–1.31) for each quintile increase in triglyceride level, and 0.86 (95% CI, 0.82–0.91) for each quintile increase in HDL-cholesterol level.

5 The findings for microvascular complications and kidney disease remained significant after adjustment for hypertension and HbA_{1c}; however, the ORs for retinopathy alone were not significant.

6 The authors suggest that the protective effect of the blood–retinal barrier against extravasation of plasma lipoproteins may account for the lack of effect on retinopathy risk.

Sacks FM, Hermans MP, Fioretto P et al (2014) Association between plasma triglycerides and high-density lipoprotein cholesterol and microvascular kidney disease and retinopathy in type 2 diabetes mellitus: a global case–control study in 13 countries. *Circulation* **129**: 999–1008

Am J Hypertens

Vitamin D and blood pressure in gestational diabetes

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓

1 Low vitamin D levels are linked to hypertension and adverse pregnancy outcomes in the general population.

2 The authors assessed the association between serum 25-hydroxyvitamin D (25[OH]D) levels and maternal blood pressure (BP) in 184 women with gestational diabetes.

3 Participants with 25(OH)D levels <30 ng/mL had higher mean systolic and diastolic BP both at the beginning and at the end of the third trimester compared to those with levels ≥30 ng/mL.

4 The correlation was not significant after adjustment for confounding factors in the cohort as a whole or in non-white women.

5 However, in white women, 25(OH)D levels were correlated with systolic BP at the beginning (r=–0.268; P=0.002) and end (r=–0.203; P=0.02) of the third trimester.

Weinert LS, Reichelt AJ, Schmitt LR et al (2014) Serum vitamin D insufficiency is related to blood pressure in diabetic pregnancy. *Am J Hypertens* **27**: 1316–20

Am J Cardiol

Weight gain predicts new-onset diabetes in statin recipients

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓

1 The authors studied patients with stable coronary artery disease and no history of diabetes to determine whether change in body weight over 1 year was predictive of subsequent new-onset diabetes (NOD) in people receiving atorvastatin 10 or 80 mg/day.

2 Of 7595 participants, 659 developed NOD over a median follow-up of 4.9 years (8.1% in the 10-mg/day group and 9.2% in the 80-mg/day group).

3 Participants who developed NOD had a significantly greater increase in body weight than those who did not (1.6 kg vs. 0.9 kg; P<0.001). This effect remained significant even after adjustment for confounding factors such as hepatic marker levels.

4 The authors conclude that even a small, easily achieved weight loss can substantially reduce the risk of NOD in people who receive statins.

Ong KL, Waters DD, Messig M et al (2014) Effect of change in body weight on incident diabetes mellitus in patients with stable coronary artery disease treated with atorvastatin (from the Treating to New Targets Study). *Am J Cardiol* **113**: 1593–8

Eur Heart J

Metabolically healthy obesity, T2D and CHD

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓

1 Up to 40% of obese people have the "metabolically healthy obese" (MHO) phenotype, characterised by good insulin sensitivity, blood pressure, and fasting glucose, lipid and inflammation profiles.

2 However, the protective effect that this phenotype may have against adverse outcomes is a matter of debate.

3 The authors compared the incidence of T2D and cardiovascular disease (CVD) in MHO, metabolically unhealthy obese (MUO) and normal-weight individuals over a 17-year follow-up.

4 Of 7122 participants, 657 (9.2%) were obese; of these, 279 (42.5%) had the MHO phenotype.

5 MHO individuals had a lower risk of T2D than MUO people; however, the risk of CVD was similar, and they were at greater risk of both T2D (hazard ratio [HR], 3.25; 95% confidence interval [CI], 2.32–4.54) and CVD (HR, 1.97; 95% CI, 1.38–2.80) compared with metabolically healthy normal-weight participants.

Hinnouho GM, Czernichow S, Dugravot A et al (2014) Metabolically healthy obesity and the risk of cardiovascular disease and type 2 diabetes: the Whitehall II cohort study. *Eur Heart J* 26 Mar [Epub ahead of print]

> *"The authors conclude that even a small, easily achieved weight loss can substantially reduce the risk of new-onset diabetes in people who receive statins."*

Cardiovasc Diabetol

Targeting multiple risk factors reduces CIMT in T2D

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓

1 Carotid artery intima–media thickness (CIMT) is a validated marker of preclinical atherosclerosis, and has been shown to be a predictor of future cardiovascular events.

2 The authors investigated whether an intensified, multiple risk factor intervention affected CIMT progression in 97 people with T2D and poorly controlled cardiovascular risk factors.

3 All participants received the intensified treatment according to Austrian national guidelines for 3 months, and were followed up after 2 years.

4 In the first 3 months, the levels of the targeted risk factors (HbA_{1c}, LDL-cholesterol and blood pressure) all improved. Although they increased slightly over the next 21 months, they remained significantly lower compared with baseline at 2 years.

5 Mean CIMT decreased by 2.6% compared with baseline at 2 years. For comparison, the natural course of CIMT would be expected to be an increase of 5.6%.

6 Notwithstanding the fact that this study was uncontrolled and that CIMT is only an indirect marker of cardiovascular risk, these results suggest that an intensive, 3-month, multi-target treatment can lower cardiovascular risk in people with T2D.

Tripolt NJ, Narath SH, Eder M et al (2014) Multiple risk factor intervention reduces carotid atherosclerosis in patients with type 2 diabetes. *Cardiovasc Diabetol* **13**: 95