Eye (2004) 18, 107–112

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Sir,

Diabetic maculopathy and lipid-lowering therapy

Chowdhury *et al*,[1] have timely reviewed this important topic. We have also comprehensively reviewed association studies (cross-sectional and prospective) and intervention studies carried out over the last 50 years[2] relating to dyslipidaemia and diabetic retinopathy (DR). Overall, as has been pointed out by Chowdhury *et al*,[1] positive associations of any grade of DR with levels of total cholesterol and triglycerides were observed. In addition, association of DR with low levels of high-density lipoprotein cholesterol (HDL-C) was also shown.[3] Further, there is a possible association of DR with insulin resistance and its components such as procoagulant factors.[3]

As emphasied by Chowdhury *et al*,[1] hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have shown beneficial effects on DR in a few trials. The review, however, does not contain a recent study carried out by our group, since it was published after acceptance of the manuscript of Chowdhury *et al*.[1] We conducted a double-blind placebo-controlled randomized trial comparing 50 patients with Type II diabetes with hypercholesterolaemia, treated with either simvastatin or placebo.[4] All patients had good glycaemic and blood pressure control and had DR characterized by nonclinically significant macular oedema. Interestingly, visual acuity worsened in seven patients in the placebo group, but none in the simvastatin group (P=0.009). Fundus fluorescein angiography and colour fundus photograph improved in one patient on simvastatin therapy, while seven patients showed worsening in the placebo group (P=0.009). Such data, albeit in a small number of patients, are supported by a considerable body of evidence showing benefits of HMG-CoA reductase inhibitors in diabetic nephropathy, another microvascular complication of diabetes mellitus.[5]

According to the current guidelines, all patients of Type II diabetes with hypercholesterolaemia should be treated with the lipid-lowering therapy; hence, possible treatment-related benefit for DR would be extended to all such patients. However, there remains a vast margin for research on this issue. For example, benefits of lipid-lowering therapy on DR could be explored on patients with normal lipid levels, hypertriglyceridemia alone, and low levels of HDL-C alone. Furthermore, therapy(ies) could be attempted which improve(s) several lipid parameters simultaneously. Finally, the role of lowering elevated lipoprotein(a) levels and ameliorating procoagulant factors remains to be investigated.

The precise mechanism(s) whereby dyslipidaemia may cause or exacerbate DR remain(s) speculative. Besides damage to endothelial cells and pericytes by oxidized low-density lipoprotein cholesterol[6] as emphasized by Chowdhury *et al*,[1] the following mechanisms may be operative; elevation of blood viscosity and alteration in the fibrinolytic system,[7] incorporation of triglycerides in the cellular membrane causing retinal leakage,[8] and basal linear deposits in Bruch's membrane.[9] Further, HMG-CoA reductase inhibitors are now known to have beneficial effects on the vascular tissues other than those because of their lipid-lowering properties. In case of DR, their antioxidant properties might protect the outer retina from the oxidative damage. Prevention of apoptosis of the retinal endothelial cells by these drugs may be an additional mechanism that may preserve vascular integrity.[10]

Unfortunately, unlike macrovascular disease, medical treatment of microvascular disease in diabetes, particularly DR, remains in the nascent stage. Given the rapid global increase in the incidence and prevalence of diabetes and morbidities because of diabetic microvascular disease, this research area deserves more attention.

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Eye (2004) **18,** 107–108. doi:10.1038/sj.eye.6700530

Sir,

Lipids, diabetic maculopathy, and cardiovascular risk

Broader messages on diabetic eye care are deducible from the review by Chowdhury *et al*[1] evaluating the role of serum dyslipidaemia in diabetic maculopathy. The evidence they have surveyed indicates that dyslipidaemia has somewhat congruously joined poor glycaemic control and hypertension as cardiovascular risk factors that affect macular health in diabetes. In contemporary practice, a characterisation of risk factors for diabetic maculopathy is of monumental importance in public health terms. Type 2 diabetes is now manifesting its explosive demography in Britain with an astonishing volume of diabetic eye disease, of which maculopathy is a foremost concern. This iatrogenic fear is generated, for example, by the many patients with advanced ischaemic diabetic maculopathy who have disease untreatable by laser. Exudative maculopathy is similarly not always responsive to laser and noticeably problematic are the larger lipid deposits (especially plaques) that form in the central macula. In some diabetic eye services in Britain, the prevalence of this fundal picture is striking. Gross lipid exudation invites the same therapeutic nihilism associated with ischaemic maculopathy, because regardless of whether the tissue insult is ischaemic or exudative, the end-organ damage becomes irredeemable. In the wake of the UKPDS, preventative strategies therefore are eminently rational and a manipulation of the lipid profile as a potential adjunct to laser seems particularly compelling.

Moreover, it is arguable that ophthalmologists should develop more than a passing interest in cardiovascular risk factors since beyond the eye these factors are a leading cause of systemic morbidity and death. After all, in counterbalance, physicians undertake retinopathy screening with modest equipment. Rather than being a perfunctory exercise, a purposeful inquiry into a patient's prevailing glycaemic control, blood pressure, and lipid status (among other factors) in an ophthalmic consultation will stimulate remedial referral patterns. Indeed, even in its simplest guise the interchange with the ophthalmologist should be an opportunity to reiterate the messages behind diabetes care to our patients. By judiciously checking blood pressure and glucose on clinical suspicion, or looking up glycaemic and lipid indices, we are not (as may be the criticism) becoming diabetologists, but rather contributing in managing an unwieldy and major public health problem. This approach ought to be the strategy for any ophthalmologist examining diabetic retinopathy and not exclusively the mantra of those providing a medical retina service. To contextualise the issue for ophthalmologists yet again, diabetic eye disease is by far the most common cause of poor vision in our society among people of working age. Since the 1970s our selectively efficacious solution for maculopathy remains a Hamletesque 'to laser or not to laser' (a stabilising intervention), and even this decision is sometimes debatable and subject to the treatment ethos of a given clinician or department.

Beyond reducing macrovascular complications, an expansion of the remit of lipid-lowering therapy in managing maculopathy would represent a highly desirable therapeutic convenience in diabetes care. A large randomised controlled trial to pass final judgement on this wishful speculation can conceivably be the next landmark study in the medical management of diabetic retinopathy.

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