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PERSPECTIVE

The role of serum lipids in exudative diabetic maculopathy: is there a place for lipid lowering therapy?

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Abstract

Diabetic maculopathy is a common complication of diabetes mellitus, characterised by macular oedema and frequently accompanied by lipid exudation. It is the major cause of loss of vision from diabetic retinopathy. There is some evidence to implicate serum lipids in exudative maculopathy; cross-sectional studies suggest that higher serum lipid levels are found in patients with macular exudates, and prospective studies have shown an increased risk of exudative maculopathy if baseline cholesterol is higher.

The treatment for diabetic maculopathy is laser photocoagulation of the pigment epithelium. With the advent of systemic lipid lowering therapy over the last decade, there may be potential for medical therapy also. There is some anecdotal evidence of the effect of lipid lowering agents (particularly statins) in reducing exudate, and a number of studies have shown that lipid lowering therapy may reduce macular exudates, but numbers in these trials are small. A randomised controlled trial is now required to investigate whether the use of systemic lipid lowering therapy is of benefit in patients with exudative maculopathy, even in the absence of dyslipidaemia.
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Introduction

Diabetic retinopathy is a major microvascular complication of diabetes, and is the commonest cause of blindness in people of working age in the Western world. Diabetic maculopathy, defined as retinopathy within one disc diameter of the centre of the macula, is a major cause of sight loss in diabetes.[1]

Diabetic maculopathy comprises two aspects: (i) retinal oedema in which fluid and lipoproteins accumulate within the retina; and (ii) macular ischaemia in which there is closure of perifoveal capillaries demonstrable on fundus fluorescein angiography. It is not known to what extent macular ischaemia contributes to the visual loss attributable to diabetic maculopathy and in this article we are limiting our discussion to macular oedema.

Macular oedema per se may be difficult to diagnose on fundoscopy, where subtle macular thickening may be responsible for insidious loss of vision. Exudates are easier to see and are a frequent component of retinal capillary leakage (termed exudative maculopathy). They do not affect vision until they encroach into the fovea at which time vision is irretrievably lost.

This article examines the role of serum lipids in exudative maculopathy and discusses the potential for systemic lipid modulation to prevent visual loss.

Epidemiology of maculopathy

The largest population-based survey of diabetic retinopathy is the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR).[2] This study examined three groups of patients with diabetes: (i) younger onset insulin-treated (mostly type 1 diabetes); (ii) older onset insulin-treated (mostly type 2); and (iii) older onset not insulin-treated (type 2). The prevalence of maculopathy was

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consistently higher in older onset insulin-treated patients rising to a peak of 25% at 15 years duration of diabetes. Only 12% of older onset patients with diabetes not on insulin had maculopathy, although it was more commonly associated with lipid exudation in this group. Eighteen per cent of younger onset diabetic patients had maculopathy and in 65% of these it was accompanied by proliferative diabetic retinopathy (PDR).

Similar prevalence data were reported in a large cross-sectional study of maculopathy from a hospital diabetic eye clinic population.[3] Fifteen per cent of type 1 and 23% of type 2 patients had maculopathy. However, in this study, maculopathy in type 1 patients was more commonly associated with non-proliferative diabetic retinopathy (NPDR) (42%) than with PDR (42% *vs* 35%). In type 2 patients, the prevalence was similar in both groups (53% NPDR, 56% PDR). In both groups the numbers with maculopathy increased with duration of diabetes.

The Melton Mowbray study describes a cross-sectional survey of the prevalence of diabetic retinopathy in a cohort of patients with diabetes residing in one town.[4] Maculopathy was present in 10% of the diabetic cohort. Risk factors identified for maculopathy in this study included age, female sex, duration of diabetes, cigarette smoking and systolic blood pressure.

Pathogenesis of diabetic maculopathy

The pathogenic mechanisms underlying diabetic retinopathy are not clear. Changes in retinal basement membrane extra-cellular matrix proteins,[5] haemodynamic changes,[6] growth factors[7] and cytokines[8] have been implicated.

A number of pathological changes occur in the retinal capillary circulation of the diabetic macula, including microaneurysm formation, capillary dilatation and closure. Macular oedema is thought to be caused principally by breakdown of the inner blood-retinal barrier. Focal oedema results from leakage across retinal microaneurysms, diffuse oedema from leakage by abnormally dilated capillaries, arterioles and venules of the macular circulation. It is postulated also that the outer retinal barrier is abnormal. Tight junctions between retinal pigment epithelial cells (RPE) may be affected by changes in structural proteins such as occludin and ZO-1[9] and transport across the RPE may be altered.

There is some evidence that vascular endothelial growth factor (VEGF) from retinal cells (eg RPE, pericytes, endothelial cells, Mueller cells, astrocytes) may be implicated in this deterioration of the blood-retinal barrier.[10] The link between the systemic abnormalities of diabetes and changes in the blood retinal barrier is poorly understood.

Are serum lipids associated with increased risk of maculopathy?

There has been considerable study of the risk factors for the development of diabetic retinopathy. In both type 1 and type 2 diabetic subjects, duration of diabetes,[3] glycaemic control,[11,12] presence of hypertension and nephropathy[13] have been associated with increased risk of retinopathy. There has been interest in the link between serum lipids and retinal exudates for 40 years.[14] A number of cross-sectional studies suggest that serum lipids may have a causative role in the development of macular exudates. Comparison of a small group of diabetic patients with severe exudative maculopathy to a group with non-exudative retinopathy demonstrated a significantly higher level of serum triglyceride in the former group, although serum cholesterol was not significantly different.[15] A case control study ($n = 26$) where patients were matched for age, gender, glycaemic control, duration and treatment of diabetes, found a trend for patients with maculopathy to have higher serum lipids over 7 years' follow-up than patients without.[16] An elevation in cholesterol has been shown in studies of exudative maculopathy in type 1 diabetes.[17] Further studies have linked LDL cholesterol with maculopathy, although numbers of patients in these studies are small.[18,19] A direct toxic effect of LDL on retinal capillary pericytes has also been demonstrated, and this toxic effect can be enhanced by LDL glycation or oxidation. In other small cross-sectional studies, lipoprotein (a) has been suggested as a risk factor for maculopathy,[20,21] although this finding is refuted on examination of a small subset of the WESDR population.[22] Improved outcome following laser photocoagulation therapy for macular oedema has been reported in subjects who have higher HDL cholesterol or normal total cholesterol.[23]

The role of dietary fat intake and its influence on exudative maculopathy has been examined. In 1965, Ernst reported reduction in retinal exudates in eight diabetic patients after 2–3 years of a carbohydrate-rich, fat-poor diet.[24] Seven year follow-up of a cohort of 149 patients randomised to a low carbohydrate or modified fat diet (rich in polyunsaturated fats) showed that patients with low levels of linoleic acid in cholesterol ester had greater risk of retinopathy.[25]

Stronger evidence for a role of serum lipids in exudative maculopathy is suggested in prospective studies. In the Early Treatment Diabetic Retinopathy

Study (ETDRS),[26] a subgroup of 2709 of the original 3711 patients had serum lipids measured. Higher baseline total and LDL cholesterol levels increased the risk of retinal exudation by two-fold at baseline. Patients with higher baseline total cholesterol, LDL cholesterol or triglycerides, had a greater risk of developing maculopathy during the course of the study. On multivariate analysis, risk of losing visual acuity was associated with severity of hard exudation, even after adjusting for macular oedema. In further analyses, elevated serum cholesterol at baseline increased the risk of visual loss by 50% compared to lower serum cholesterol levels. These findings have been supported by examination of a subgroup of the WESDR cohort.[27] Increased total cholesterol was noted in patients with increased severity of retinopathy and hard exudate.

One recent study of Age-related Macular Degeneration (AMD) suggests that statin therapy does have a protective role against the development of AMD.[28] In this cross-sectional survey, it was noted that statin use was associated with less AMD, possibly due to reductions in basal linear deposits in Bruch membrane or anti-oxidant effects.

These studies all suggest a causal link between exudative maculopathy in diabetic subjects, and their prevailing lipid profile.

Therapy to improve diabetic maculopathy

The established treatment for exudative diabetic maculopathy is laser photocoagulation, which is sight preserving.[29–31] More recently, surgical therapy, such as pars planar vitrectomy, has been advocated.[32] A number of other therapies have been suggested as effective particularly in severe exudation. Loss of negatively charged proteoglycans such as heparan sulphate from the retinal basement membrane has been suggested as leading to increased vascular permeability.[33] It was this observation that has led to a trial of danaparoid sodium, a proteoglycan molecule, in patients with diabetic nephropathy.[34] On retrospective review of these patients, it was noted that significant improvement in macular hard exudates occurred during 6 weeks of therapy with danaparoid sodium.[35] This small study has yet to be reproduced in a large randomised trial. More recently, calcium dobesilate has been suggested as reducing vascular leakage in diabetic retinopathy by reducing microvascular permeability and also having an anti-oxidant effect.[36] A small randomised trial of the drug, however, has not demonstrated any beneficial effect on reducing progression of retinopathy.[37] Anecdotally, treatment of renal failure associated anaemia with erythropoietin has also resulted in improvement in hard exudation,[38] as has heparin-induced extra-corporeal dialysis.[39]

Lipid lowering therapy in exudative maculopathy

Statin therapy has been proven to reduce cardiovascular events in patients with dyslipidaemia, both in the primary,[40] and secondary[41] prevention settings. More recently, fibrate therapy has also demonstrated reduction in cardiovascular events in patients with low HDL and high triglyceride levels post myocardial infarct.[42] These drugs are thus proven to reduce cardiovascular disease in the presence of dyslipidaemia.

Interestingly, these trials of lipid lowering therapy in diabetic maculopathy were undertaken before any significant evidence of a role for lipids in maculopathy was available. These small trials of either clofibrate or atromid in exudative maculopathy have suggested that a reduction in macular hard exudates could be achieved, but with little improvement in visual acuity.[43,44] Of note, however, is that the visual acuity of the patients in these trials was poor at the outset, and hence a significant improvement with lipid lowering therapy may not be expected. A more recent German pilot study used etofibrate in patients with type 2 diabetes and type 2b hyperlipoproteinaemia with diabetic maculopathy.[45] Clear regression of macular exudates was seen in seven of 10 patients in 6 months. Two small pilot studies have used statin therapy in diabetic retinopathy.[46,47] In one pilot study, six patients with exudative maculopathy were treated with pravastatin, which lowered their total and LDL cholesterol by 40%. Over one year, an improvement in hard exudates in all six patients, with reduced microaneurysms in four patients was observed, and acuity improved in one patient.

Conclusions and further studies

Lipid exudation at the diabetic macula is the result of increased vascular permeability, plus a dysfunctional outer blood-retina barrier and retinal pigment epithelium. There is now compelling evidence that serum lipoproteins have a major role in exudative maculopathy in patients with diabetes, such that increasing total or LDL cholesterol is accepted as a risk factor for maculopathy.

Type 2 diabetes is characterised by hyperglycaemia. It is now widely recognised that disordered lipid metabolism and a tendency to angiopathy are also major characteristics of diabetes. Recent advances in lipid lowering therapy have presented us with the

opportunity to intervene effectively in dyslipidaemia with the use of either statins or newer fibrates. Whilst primary prevention studies on macrovascular disease specifically in diabetic patients are ongoing, the recently published Joint British Societies guidelines suggest that lipid lowering therapy should be instituted on the basis of Coronary Heart Disease Risk, calculated using the Framingham Equation.[48]

The presence of exudative maculopathy is not currently an indication for institution of lipid lowering therapy. It is not known whether exudative maculopathy may improve with the use of a statin or a fibrate, even in the absence of significant dyslipidaemia, and whether this improvement leads to improved visual outcome. One study of fenofibrate in patients with diabetes has included retinal photography, and hence may contribute to the debate. It is clear, however, that a randomised controlled trial of lipid lowering therapy in patients with exudative maculopathy is required to answer these questions.

The St Vincent declaration some 10 years ago set out a reduction in visual loss of 30% as a major aim of diabetes care over the coming decade.[49] Whilst improving anti-hyperglycaemic and anti-hypertensive therapy is likely to reduce the incidence of maculopathy, reducing the progression of exudative maculopathy to marked visual loss must be also considered a priority, and lipid lowering therapy has the potential to augment laser photocoagulation in reducing visual loss in exudative maculopathy.

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