

# Retinal vein occlusion and the prevalence of lipoprotein abnormalities

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**SUMMARY** Ninety-nine patients with retinal vein occlusion (40 with central, 59 with branch vein occlusion) were investigated for the prevalence of associated diseases for comparison with an age-matched control group. There was a significantly increased prevalence of hyperlipidaemia ( $p < 0.001$ ) and hypercholesterolaemia ( $p < 0.001$ ) in the group with branch retinal vein occlusion and of hyperlipidaemia ( $p < 0.001$ ) and hypercholesterolaemia ( $p < 0.02$ ) in the group with central retinal vein occlusion compared with controls. An increased prevalence of hypertriglyceridaemia ( $p < 0.001$ ) was also found in patients with central vein occlusion. Other associations were noted (hypertension and oestrogen therapy). Increased serum cholesterol concentrations were found in patients with central vein occlusion ( $p < 0.05$ ) and branch vein occlusion ( $p < 0.001$ ) compared with controls, and similar tendencies were noted for levels of LDL and HDL cholesterol. Patients with central vein occlusion also had raised levels of serum triglyceride ( $p < 0.001$ ) and VLDL-triglyceride ( $p < 0.05$ ). The occurrence of both central and branch vein occlusions may be associated with an increased prevalence of hyperlipidaemia and hypertension. Increase of serum lipids may contribute to the aetiology of vein occlusion by altering plasma viscosity or affecting platelet function.

Occlusion of the retinal veins (either branch or central) is an important cause of visual loss, particularly in middle age.<sup>1</sup> Although the cause of this condition is unclear, it is frequently found in association with other diseases, such as hypertension or diabetes mellitus. Several recent studies have suggested that retinal vein occlusion may also occur more frequently in patients with hyperlipidaemia. For example, there was a 2- to 4-fold greater prevalence of hypercholesterolaemia or hypertriglyceridaemia in a group of 116 patients with central retinal vein occlusion than in a control population taken from published reports.<sup>2</sup> Possible explanations for the association of retinal vein occlusion with hyperlipidaemia may be through effects on plasma viscosity or alterations in platelet function, with release of platelet-specific proteins (B-thromboglobulin and platelet factor 4), thereby predisposing to platelet aggregation and thrombosis. These possibilities are of course not exclusive.

However, not all lipoprotein fractions have similar effects on vascular disease. Epidemiological studies

have suggested that high-density lipoprotein (HDL) cholesterol may protect against macrovascular disease, whereas low-density lipoprotein (LDL) cholesterol may predispose to it.<sup>3,4</sup> Similar consideration may also apply to lipoproteins and microvascular disease.

For this reason we have studied individual lipoprotein fractions, with other possible predisposing factors, in a group of patients with retinal vein occlusion for direct comparison with an age-matched population.

## Patients and methods

Ninety-nine patients with retinal vein occlusion (40 with central retinal vein occlusion and 59 with branch retinal vein occlusion) were investigated serially with no prior selection at Moorfields Eye Hospital. The diagnosis of retinal vein occlusion, apart from suggestive clinical history and funduscopy, was confirmed by fluorescein angiography. Further clinical examination included a search for the presence of large-vessel disease (angina, claudication, cerebrovascular accidents, and transient ischaemic attacks), alcohol consumption, smoking habits, and associated

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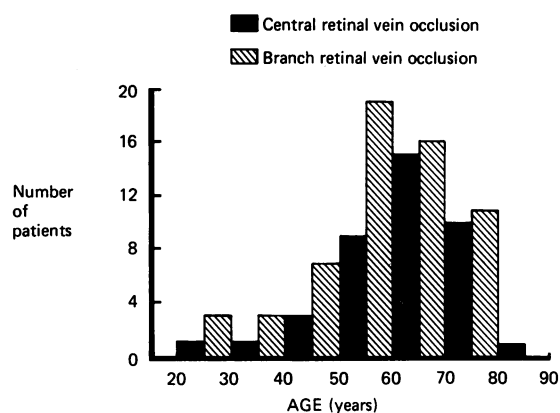


Fig. 1 Age distribution of 99 patients presenting with retinal vein occlusion.

drug therapy. After full clinical examination (by P.M.D.) the following investigations were performed: oral glucose tolerance test with a 75 g load, liver function tests, full haematological profile, plasma viscosity, electrocardiography, and chest radiology.

The comparison group for this study was recruited from hospital outpatients attending our clinics with treated essential hypertension (n=33) and hospital staff (n=7) who had no evidence of retinal venous occlusion. The same investigations were performed as in the group with retinal vein disease except for a full glucose tolerance test, where blood glucose estimations were taken with the fasting lipid profile.

Glucose intolerance and diabetes mellitus were diagnosed by the criteria of the British Diabetic

Association recommendations.<sup>5</sup> Hypertension was defined as 3 consecutive blood pressure recordings of systolic greater than 160 mmHg and diastolic greater than 95 mmHg or when a patient was already established on antihypertensive drug therapy.

Plasma viscosity was measured by a Coulter-Harkness viscometer at 25°C (normal range 1.60-1.9 centipoise).<sup>6</sup> The electrocardiograms were coded and analysed for ischaemic heart disease, left ventricular hypertrophy, and bundle branch block by the Minnesota code.

Serum cholesterol and triglyceride concentrations were measured by semiautomated fluorimetric techniques (Technicon Instruments Co. Ltd.), Liebermann-Burchard's reagent being used for cholesterol (normal range: 4.5-6.7 mmol/l) and Cramp and Robertson's method for triglyceride (normal range: male, 0.6-2.1, female 0.6-1.8 mmol/l).<sup>7</sup> HDL cholesterol was measured in the supernatant fraction following precipitation of very low-density lipoprotein (VLDL) and LDL by heparin (250 units/50 µl) and 1 M manganese chloride (50 µl). VLDL cholesterol and triglyceride was measured after precipitation by sodium dodecyl sulphate (100 g/l in 0.15 M sodium chloride; 75 µl). LDL cholesterol was obtained by subtracting the sum of HDL and VLDL cholesterol from the total serum cholesterol.

The fluorescein angiograms of 33 patients with branch retinal vein occlusion were scored in single-blind manner for severity of capillary leakage, closure, and the presence of neovascularisation into 4 categories (nil=0, mild=1, moderate=2, severe=3, by A.M.H.) giving a measure of the severity of the retinal vein occlusion (range 1 to 10). Statistical analyses were performed by nonparametric tech-

Table 1 Clinical and biochemical details of patients with retinal vein occlusion and the control group

	Sex	Mean age (yr)	Mean ideal weight (%)	Mean blood pressure (mmHg)		Mean fasting blood glucose (mM)	Mean serum cholesterol (mM)	Mean serum tri-glyceride (mM)	LDL cholesterol (mM)	HDL cholesterol (mM)	VLDL tri-glyceride (mM)	Plasma viscosity (centipoise)	Number of patients with ischaemic heart disease on ECG	Number of smokers
				Systolic	Diastolic									
Control (n=40)	M30	52.2 ± 13.4	113.3 ± 14.4	147.4 ± 22	90.5 ± 14.2	5.73 ± 2.1	5.2 ± 1.36	1.33 ± 0.52	3.32 ± 1.32	1.20 ± 0.52	0.50 ± 0.42	1.73 ± 0.09	10 (25%)	12 (30%)
Central retinal vein occlusion (n=40)	M25	62.6 ± 11.2	111.7 ± 13.8	157.7 ± 31.5	87.6 ± 11.5	5.7 ± 1.8	5.64* ± 1.61	1.62*** ± 1.03	3.58 ± 1.33	1.35 ± 0.50	0.58* ± 0.4	1.72 ± 0.1	12 (30%)	13 (32.5%)
Branch retinal vein occlusion (n=59)	M39	58.3 ± 13.3	111.8 ± 14.2	161.4*** ± 30.3	91.6 ± 17.5	5.1 ± 1.1	6.0*** ± 1.6	1.35 ± 0.8	3.84** ± 1.55	1.5** ± 0.57	0.59 ± 0.69	1.70 ± 0.09	17 (29%)	25* (42.4%)

Values are mean ± SD. \*p<0.05. \*\*p<0.01. \*\*\*p<0.001. Statistics by chi-squared test. HDL=high-density lipoprotein. LDL=low-density lipoprotein. VLDL=very low-density lipoprotein.

niques (chi-squared test, binomial *p* test),<sup>8</sup> and correlations were made by the Pearson linear correlation coefficient.

## Results

The mean age of onset of both branch and central retinal vein occlusion (55-65 yr) was similar and is presented in Fig. 1. Table 1 presents the mean serum lipids, lipoproteins, and other variables of the 3 groups under study. Higher serum cholesterol concentrations were found in patients with central retinal vein occlusion ( $p < 0.05$ ) and branch retinal vein occlusion ( $p < 0.001$ ) than in the control group and similar tendencies were noted for the levels of LDL and HDL cholesterol. Patients with central retinal vein occlusion also had raised levels of serum triglyceride ( $p < 0.001$ ), but this was not so marked when VLDL triglyceride was measured.

The prevalence of macrovascular disease, as recorded by evidence of ischaemic heart disease on the electrocardiograph, was similar among the groups studied, but the patients with branch retinal vein occlusion had a higher mean systolic blood pressure ( $p < 0.001$ ) than other groups.

The prevalence of other diseases associated with retinal vein occlusion is presented in Table 2. There was a significantly higher prevalence of hyperlipidaemia ( $p < 0.001$ ) and hypercholesterolaemia ( $p < 0.01$ ) in both retinal vein occlusion groups than in the comparison group. However, an increased prevalence of hypertriglyceridaemia ( $p < 0.001$ ) was also found in patients with central retinal vein occlusion. Unfortunately it was not possible to compare the prevalence of hypertension in the retinal vein occlusion groups with that of the control group, as the latter were mainly drawn from a hypertension clinic (see 'Methods'). However, 41 out of 99 patients with retinal vein occlusion were found to have essential hypertension. Retinal vein occlusion was the clinical presentation in 16 patients with previously undiagnosed hypertension and in 25 with established hypertension on drug therapy. Systolic blood pressure was significantly higher ( $p < 0.001$ ) in the established hypertensive patients on drug therapy ( $176.8 \pm 27.7$

Table 2 Prevalence of associated diseases in retinal vein occlusion

Associated disease	Comparison group (n=40)	Branch retinal vein occlusion (n=59)	Central retinal vein occlusion (n=40)
Hyperlipidaemia	15% (6)	28.8% (17)**	32.5% (13)**
Hypercholesterolaemia	7.5% (3)	23.7% (14)**	22.5% (9)*
Hypertriglyceridaemia	7.5% (3)	8.5% (5)	25% (10)**
Hypertension	82.5% (33)	44% (26)	37.5% (15)
Diabetes mellitus	9.5% (4)	10% (6)	15% (6)
Glucose intolerance	—	15.3% (9)	17.5% (7)
Oestrogen therapy	—	3.4% (2)	5% (2)
No associated disease or drug therapy	—	37.3% (22)	22.5% (9)

\* $p < 0.02$ . \*\* $p < 0.001$  by nonparametric statistics (chi-squared and binomial *p* test).

mmHg) and in the previously undiagnosed hypertensive patients ( $193.1 \pm 19.6$  mmHg) than in the treated hypertensives in the comparison group ( $152.3 \pm 20.5$  mmHg,  $n = 33$ ). It was also of interest that 4 patients presenting with retinal vein occlusion (2 with central and 2 with branch retinal vein occlusion) were taking oestrogen therapy, one patient was on an oral contraceptive, and 3 were on oestrogen therapy for post-menopausal symptoms when they presented at our clinic.

There were no significant differences in the mean plasma viscosities of the 3 groups studied as shown in Table 1. However, the association of raised levels of cholesterol, triglyceride, and LDL cholesterol with retinal vein occlusion may be related to alterations in the plasma viscosity, as shown by the correlations found between these parameters in Table 3. Total serum proteins and serum globulins were positively correlated with plasma viscosity ( $p < 0.001$ ), but weaker positive correlations were found with total serum cholesterol ( $p < 0.01$ ), LDL cholesterol ( $p < 0.01$ ), VLDL cholesterol ( $p < 0.05$ ), and total serum triglyceride ( $p < 0.05$ ). A significant positive correlation was also found in patients with branch retinal vein occlusion between the fluorescein score and serum LDL cholesterol levels ( $r = +0.492$ ,  $n = 33$ ,  $p < 0.01$ ) and a weaker correlation with total serum cholesterol ( $r = +0.39$ ,  $n = 33$ ,  $p < 0.05$ ).

Table 3 Linear correlation coefficients between serum lipid parameters, serum proteins with plasma viscosity in patients with retinal vein occlusion

		Total serum cholesterol (mM)	Total serum triglyceride (mM)	LDL cholesterol (mM)	VLDL cholesterol (mM)	Serum globulins (g/l)	Serum total proteins (g/l)
Plasma viscosity (centipoise)	Correlation coefficient	0.297	0.230	0.277	0.223	0.601	0.36
	Number of patients	99	99	97	97	90	91
	Significance	<0.01	<0.05	<0.01	<0.05	<0.001	<0.001

## Discussion

Our results suggest that hyperlipidaemia is more likely to occur in patients with retinal vein occlusion than in an age-matched comparison group. Serum cholesterol and LDL cholesterol showed a stronger association with retinal vein occlusion than serum triglyceride or VLDL triglyceride. However, mean serum HDL cholesterol concentrations were higher in the branch retinal vein occlusion group ( $p < 0.01$ ) but were also raised in patients with central retinal vein occlusion. HDL lipoprotein can be fractionated into 2 components, HDL-2 and HDL-3, with different lipid and apoprotein compositions. It has previously been shown that the HDL-2 subfraction related more strongly to the occurrence of large-vessel disease,<sup>9</sup> and it is possible that subfractions of HDL may show stronger associations with microvascular disease, such as retinal vein and arteriolar occlusions, than total HDL cholesterol.

Of the other associated factors smoking habits, frequency of large-vessel disease, and glucose intolerance may also be determinants, though only minor differences were observed between the retinal vein occlusion and control groups.

Systolic blood pressure in patients with branch retinal vein occlusion was significantly higher than in the comparison group, who were predominantly treated essential hypertensives. This suggests that hypertension may be a major aetiological factor. It is further supported by the high prevalence of hypertension in our patients with branch retinal vein occlusion and by the finding of left ventricular hypertrophy in 6 of the 26 hypertensive patients with branch retinal vein occlusion, compared with only 2 of the 33 hypertensive patients in the comparison group. Systolic blood pressure was also raised in patients with established hypertension on drug therapy. There was also a higher incidence of hypertension in patients with central retinal vein occlusion (37.5%) than that quoted in the normal population (for example, 21.2%).<sup>10</sup>

The pathogenesis of retinal vein occlusion is still in dispute. Possible aetiological factors include venous thrombosis or endothelial swelling and constriction, which may predispose to microvascular thrombosis.<sup>11</sup> Ring *et al.*<sup>12</sup> have also suggested that whole blood viscosity may be a contributory factor, as they found a close correlation between the whole blood viscosity and the severity of retinal ischaemia on fluorescein angiography in patients with branch and central retinal vein occlusion.

There were no statistical differences in the mean plasma viscosities among the groups studied, but there was a significant correlation between plasma viscosity and plasma lipids, particularly total and

LDL cholesterol, which, like serum globulins and total proteins, clearly contribute to the plasma viscosity and, if increased, may predispose to a 'hyperviscosity' syndrome. LDL cholesterol and total serum cholesterol were also significantly correlated with the fluorescein score, which gives a measure of the severity of the retinal vein occlusion. These results in conjunction with the significantly raised serum LDL cholesterol and total serum cholesterol suggest that the major cholesterol-containing lipoproteins may contribute to the pathogenesis of retinal vein occlusion. Alternative explanations such as the effects of lipoproteins on the platelet release reaction that predisposes to aggregation are under current investigation in our laboratory.

We conclude therefore that both central and branch retinal vein occlusion are associated with an increased prevalence of hyperlipidaemia, hypertension, and glucose intolerance. Total serum cholesterol and LDL cholesterol are raised in patients with retinal vein occlusion and may contribute to the aetiology of this condition. HDL cholesterol levels are higher than in the comparison group and do not appear to be protective for the retinal microcirculation. Any patients with retinal vein occlusion should be investigated for underlying hypertension, hyperlipidaemia, and diabetes mellitus and appropriate therapy instituted.

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