

# Medical conditions underlying recurrence of retinal vein occlusion

P M DODSON,<sup>1,2</sup> A J KUBICKI,<sup>2</sup> K G TAYLOR,<sup>2</sup> AND E E KRITZINGER<sup>1</sup>

From the <sup>1</sup>Department of Medical Ophthalmology, Birmingham and Midland Eye Hospital, and the <sup>2</sup>Clinical Investigation Unit, Dudley Road Hospital, Birmingham

**SUMMARY** Seventeen patients with recurrent retinal vein occlusion were investigated for underlying medical conditions and compared with 61 patients with single retinal vein occlusion (26 with central, 35 with branch vein occlusion). The two study groups were comparable for age, sex, and weight. Patients with recurrence had a significantly increased prevalence rate of hypertension (88% versus 48%:  $p < 0.01$ ), with a trend to increased hyperlipidaemia (47% versus 33%) compared with patients with a single episode. A significantly raised mean systolic ( $p < 0.05$ ) but not diastolic blood pressure was found in patients with recurrence. Other cardiovascular risk factors in patients with recurrence were also found and included lower mean levels of high density lipoprotein (HDL)-cholesterol ( $p < 0.02$ ) and the HDL<sub>2</sub> subfraction ( $p < 0.001$ ), and a significantly increased proportion of patients with regular alcohol intake ( $p < 0.01$ ). We conclude that hypertension and hyperlipidaemia with an increase in other cardiovascular risk factors are commonly found in patients with recurrent retinal vein occlusion and may therefore be important aetiological factors. The possible benefits of treatment of these underlying conditions to prevent recurrence need to be assessed in well designed prospective studies.

Retinal vein occlusion is a common cause of visual loss in the United Kingdom. Its exact aetiology is unclear and therefore medical treatment is unsatisfactory. Management of it is aimed at identifying and treating the complications of retinal vein occlusion, and underlying medical conditions, for example, hypertension, hyperlipidaemia, diabetes mellitus, enhanced platelet activity, or hyperviscosity syndromes.<sup>1-5</sup>

However, reports have suggested that 15% of patients who have had a single retinal vein occlusion will go on to have another, commonly in the previously non-affected eye, with a consequent disastrous visual outcome.<sup>6</sup> Patients with recurrent retinal vein occlusion have not been studied separately from those with single retinal vein occlusion, and so no data are available on why patients have a recurrence or which ones will do so.

We have therefore performed a study to identify the prevalence of medical conditions associated with recurrent retinal vein occlusion as compared with cases of single occlusion. Special emphasis has been

paid to cardiovascular risk factors, including hypertension, hyperlipidaemia, and lipoprotein levels. These include the positively associated low density lipoprotein (LDL) and the negatively associated high density lipoprotein (HDL)-cholesterol and one of its subfractions HDL<sub>2</sub>.<sup>7</sup>

## Patients and methods

Sixty-one patients with single retinal vein occlusion (26 with central and 35 with branch retinal vein occlusion) and 17 patients with recurrent retinal vein occlusion were investigated serially with no prior selection at Birmingham and Midland 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 and a history of current drug therapy. After full clinical examination the following investigations were performed: full haematological profile, liver function tests, fasting lipid profile, and blood sugar.

Blood pressure was recorded after five minutes' rest in the sitting and supine position on an Accuson

Correspondence to Dr P M Dodson, Clinical Investigation Unit, Dudley Road Hospital, Birmingham B18 7QH.

sphygmomanometer and the mean recorded. Diastolic pressure was recorded at the fifth Korotkoff phase.

Hypertension was defined as three consecutive blood pressure recordings of systolic greater than 160 mmHg and diastolic greater than 95 mmHg or when a patient was already established on anti-hypertensive drug therapy. Hyperlipidaemia was defined as a fasting serum cholesterol level greater than 7.1 mmol/l or serum triglyceride level greater than 2.1 mmol/l.

Serum cholesterol and triglyceride were measured by standard semiautomated techniques. HDL-cholesterol was measured in the supernatant fraction following precipitation of very low density lipoprotein (VLDL) and LDL by heparin (250 units/50  $\mu$ l) and 1 M manganese chloride (50  $\mu$ l) (coefficient of variation 2%).<sup>8</sup> Further precipitation of the supernatant containing HDL with 100  $\mu$ l low molecular weight dextran sulphate (14.3 g/l) as reported by Ferns *et al.* allowed measurement of the HDL<sub>3</sub> subfraction.<sup>9</sup> The HDL<sub>2</sub> cholesterol level was calculated by subtraction of HDL<sub>3</sub> level from the total

HDL cholesterol level. The results of HDL<sub>2</sub>-cholesterol measured by precipitation correlated well with results of preparative ultracentrifugation ( $r=+0.978$ ,  $p<0.001$ ).<sup>10</sup> VLDL-cholesterol was measured after precipitation by sodium dodecyl sulphate (100 g/l in 0.15 M sodium chloride; 75  $\mu$ l). LDL-cholesterol was obtained by subtracting the sum of HDL and VLDL cholesterol from the total serum cholesterol.

Statistics were by unpaired *t* test and the  $\chi^2$  test with Yates's correction factor.

## Results

The clinical details of the patients studied are shown in Table 1. The two groups were well matched for clinical details apart from the smaller number of patients in the recurrence group. This difference was expected owing to the low incidence of recurrence in those patients with single retinal vein occlusion.

Table 2 presents the prevalence of associated diseases in the two groups. The prevalence rates of associated medical conditions in the group of patients with single retinal vein occlusion used for comparison in this study were similar to those of larger series.<sup>2,3</sup>

There was a significantly increased prevalence rate of hypertension ( $p<0.01$ ) and a trend to an increase in the prevalence of hyperlipidaemia in those patients with recurrence compared with those with a single retinal venous event. The prevalence rates of hypercholesterolaemia and hypertriglyceridaemia showed an increase in the recurrent group, though this did not reach statistical significance. No significant differences were also observed (Table 3) between mean total serum cholesterol triglyceride and LDL-cholesterol levels, but mean total HDL-cholesterol levels ( $p<0.02$ ) were significantly reduced in the recurrent group. This difference was due to a reduction in mean HDL<sub>2</sub>-cholesterol levels ( $p<0.001$ ) and not in HDL<sub>3</sub> levels.

There was no difference between the groups with

Table 1 Clinical details of patients studied with a single episode and recurrent vein occlusion

Group		Form of retinal vein occlusion	Mean age (yr)	Mean weight (kg)
Single retinal vein occlusion (n=61)	27M	BRVO (35)	61.0	70.1
	34F	CRVO (26)	$\pm 13.6$	$\pm 12.4$
Recurrent retinal vein occlusion (n=17)	9M	Bilateral BRVO (6)	65.94	72.42
	8F	Bilateral CRVO (6)	$\pm 9.63$	$\pm 15.6$
		Central and BRVO (5)		

BRVO and CRVO=Branch and central retinal vein occlusion respectively.

Table 2 Prevalence rates of associated conditions in patients with single and recurrent retinal vein occlusion

	Hypertension	Hyperlipidaemia	Hypercholesterolaemia	Hypertriglyceridaemia
Recurrent retinal vein occlusion (n=17)	88% (15)	47% (8)	35% (6)	24% (4)
Significance	$p<0.01$	NS	NS	NS
Single retinal vein occlusion (n=61)	48% (29)	33% (20)	28% (17)	15% (9)

Statistics by the  $\chi^2$  test. NS=not significant.

Table 3 Serum lipid and lipoprotein levels in patients with single and recurrent retinal vein occlusion

	Mean serum cholesterol (MM)	Mean serum triglyceride (MM)	Mean HDL cholesterol (MM)	Mean HDL <sub>2</sub> cholesterol (MM)	Mean HDL <sub>3</sub> cholesterol (MM)	Mean LDL cholesterol (MM)
Recurrent retinal vein occlusion (n=17)	6.36 ±1.6	1.69 ±0.74	1.24* ±0.3	0.30† ±0.11	0.93 ±0.31	3.35 ±1.12
Single retinal vein occlusion (n=61)	6.3 ±1.4	1.37 ±0.7	1.46 ±0.3	0.52 ±0.24	0.95 ±0.25	3.17 ±1.26

Values are mean ± SD. \*p<0.02. †p<0.001. HDL=high-density lipoprotein. LDL=low-density lipoprotein.

regard to the number of current cigarette smokers (23.5 versus 22.9%). In contrast, there was a significantly greater proportion of patients with a current regular alcohol intake (>7 g of alcohol/day) in the recurrent group than in the group with single retinal vein occlusion (47% versus 13%; p<0.01).

Further analysis with regard to blood pressure in the two groups (Table 4) revealed a significant increase in mean systolic blood pressure (p<0.01) in the recurrent group, but the minor increase in diastolic blood pressure did not reach statistical significance. Table 5 analyses those patients with hypertension in the two groups. Of 15 patients with hypertension in the recurrent group seven were newly diagnosed and eight were on prior antihypertensive medication. However, to emphasise the possible importance of good blood pressure control only three patients on prior medication had normal blood pressure recordings.

**Discussion**

The striking result in this study is the finding of such a high prevalence rate of hypertension (87%) in those patients with recurrent retinal vein occlusion. This finding, in conjunction with the raised mean levels of

blood pressure and the high number of patients with poor control of hypertension, lends further strong support to the view that hypertension is a major aetiological factor. This is supported by the recent observation of poorly controlled hypertension in five of eight patients who developed recurrence of retinal vein occlusion during a five- to 10-year follow-up period.<sup>11</sup> These observations may also have implications with regard to the life expectancy of patients with retinal vein occlusion, as in a 10-year prospective study of 226 patients the proportion with a vascular cause of death (cardiac or cerebral) was about double that expected from mortality statistics compiled for England and Wales.<sup>6</sup> In view of the evidence that drug treatment of hypertension may reduce some hypertensive complications, particularly cerebrovascular episodes,<sup>12</sup> it seems likely that good control of hypertension should reduce the mortality of patients with retinal vein occlusion from vascular causes and possibly recurrence of retinal vein occlusion. That retinal vein occlusion and cerebrovascular disease have a common aetiology in hypertension is therefore clear, but the situation differs in patients of different ethnic groups. For example, it has recently been noted that retinal vein occlusion, particularly the central form, is rarely seen

Table 4 Mean blood pressure levels in the patients with single and recurrent retinal vein occlusion

	Mean systolic blood pressure (mmHg)	Mean diastolic blood pressure (mmHg)
Recurrent retinal vein occlusion (n=17)	175* ± 30.2	92.1 ±10.0
Single retinal vein occlusion (n=61)	156.6 ± 26.4	88.6 ±10.2

Figures are mean ± SD. \*p<0.05 by unpaired t test.

Table 5 Hypertension in the two groups of patients with retinal vein occlusion

Hypertensive group	Percentage and number of patients		
	Newly diagnosed	On prior antihypertensive medication	On prior antihypertensive medication but still hypertensive
Recurrent retinal vein occlusion (n=15)	47% (7)	53% (8)	63% (5)
Single retinal vein occlusion (n=29)	38% (11)	62% (18)	44% (8)

in blacks in two major ophthalmological centres serving large West Indian populations,<sup>13</sup> but it is this group who have been reported to have the highest prevalence of hypertension associated with a high incidence of cerebrovascular disease.<sup>14</sup> Furthermore, hypertension is often severer in blacks than in the white community, in whom retinal vein occlusion is evidently more common.<sup>14</sup>

The exact mechanism of retinal venous damage by hypertension is unclear but possibilities include increased inflammatory activity, which has been demonstrated in hypertensive patients with retinal vein occlusion,<sup>15 16</sup> or indirect vascular damage to the retinal vein. This in turn may lead to vascular degeneration, with deposition of platelet aggregates.

Other cardiovascular risk factors for recurrence found in this study include an increased prevalence of hyperlipidaemia and reduced levels of HDL-cholesterol and its subfraction HDL<sub>2</sub>. These findings might just express the presence of generalised vascular disease per se, but this is doubtful, as the prevalence of hyperlipidaemia appears to be significantly greater in patients with retinal vein occlusion than in control subjects with the same prevalence of overt macrovascular disease.<sup>3</sup> Furthermore a significant positive relationship has been demonstrated between increasing serum cholesterol levels and the severity of retinal venous lesion on fluorescein angiograms.<sup>3</sup> It would therefore appear that hyperlipidaemia may also be aetiological in single and recurrent retinal vein occlusion and that, in patients with a single retinal venous event, hyperlipidaemia and a low serum HDL-cholesterol might be more at risk of recurrence.

It is also of interest that there was a significant increase in the number of patients with a regular alcohol intake in the recurrence group. This may be a factor in the aetiology of the increased hyperlipidaemia and hypertension observed in this group. Smoking, another important cardiovascular risk factor, was not different in the two study groups.

Although no conclusions on the benefit of treating associated conditions to prevent recurrence can be made, this study does suggest the possibility that treatment of hypertension and hyperlipidaemia in these patients might be of value to prevent recurrence. This hypothesis has indeed recently been tested but in a non-controlled retrospective study of 22 hypertensive patients with retinal vein occlusion. The results were disappointing in that recurrence was not prevented, but this may well be due to the poor hypotensive control achieved by drug treatment and the failure to include treatment for hyperlipidaemia in this study.<sup>17</sup>

We conclude that hypertension and hyperlipidaemia, with an increase in other cardiovascular risk factors, are found in patients with recurrent retinal vein occlusion. These may therefore be important aetiological factors, but the exact mechanisms and the possible benefits of treatment need to be assessed in well designed prospective studies.

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