Secondary hyperlipidaemia

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The secondary hyperlipidaemias occur remarkably frequently, and the underlying cause of high serum lipid levels will often be missed if it is not actively sought. Diagnosis is important because the lipid abnormality responds to treatment of the primary disorder in most cases; notable exceptions to this, however, are the hyperlipidaemias associated with gout and chronic renal failure.

The conditions regularly associated with hyperlipidaemias are listed in the table. There is no lipoprotein pattern which is specific for any one of these, and almost any pattern may occur in every condition; the pattern may even vary from time to time in the same patient.

Diabetes ¹
Alcoholism ¹
Chronic renal failure ¹
Nephrotic syndrome
Hypothyroidism
Gout ¹
Obstructive liver disease
Oestrogens ¹
Hypopituitarism
Acromegaly
Cushing's syndrome
Addison's disease
Pregnancy
Dysglobulinaemias
Porphyria ²
Idiopathic hypercalcaemia ²
Vitamin D intoxication ²
Glycogen storage disease ¹
Gram-negative septicaemia ¹

Table Causes of secondary hyperlipidaemia

¹Raised triglyceride levels chiefly

²Raised cholesterol levels chiefly

Secondary hyperlipidaemia may be detected during the investigation of the primary condition or during the routine investigation of a hyperlipidaemic patient. Xanthomas may be the presenting feature as may be atherosclerotic complications if the abnormality is of long standing.

Diabetes Mellitus

Gross lipaemia, often with an increase in both chylomicrons and very-low-density lipoprotein

(VLDL), eruptive xanthomas, and lipaemia retinalis, is a rare complication of uncontrolled diabetes (Bagdade, Porte, and Bierman, 1967). Much more frequently diabetics are found to have moderate to slight elevation of serum triglyceride levels due to an increase of very-low-density lipoprotein. Chance, Albutt, and Edkins (1969) found two-thirds of 135 newly diagnosed diabetic children to have hyperlipidaemia and a similar prevalence was found in untreated diabetics by Hayes (1972). A lower incidence has, however, been suggested by two studies at the Hammersmith Hospital (Elkeles, Lowy, Wyllie, Young, and Fraser, 1971; Lewis, Mancini, Mattock, Chait, and Fraser, 1972b).

The pathogenesis of diabetic hypertriglyceridaemia is not clear. Impaired removal of triglyceride from the plasma, excessive secretion of VLDL, or a combination of both could lead to expansion of the plasma triglyceride pool.

As the concentration and turnover of free fatty acids is elevated in most uncontrolled diabetics (Bierman, Dole, and Roberts, 1957; Lewis *et al.*, 1972b) an increased hepatic uptake of free fatty acids is to be expected. This would favour enhanced triglyceride synthesis and VLDL secretion. However, secretion of VLDL by the liver is dependent on insulin (Van Haarken, Brown, and Heimberg, 1967) and can therefore be expected to be reduced in diabetes. The net effect of these apparently opposing influences in the intact animal was studied in pancreatectomized dogs by Basso and Havel (1970), who showed an overall reduction of VLDL secretion. As many diabetics have some circulating insulin, extrapolation of these results to the diabetic patient may not be justified.

Removal of triglyceride from the circulation occurs largely in the adipose tissue and muscle where triglyceride, carried as chylomicrons and VLDL, is hydrolyzed by lipoprotein lipase. This enzyme seems to be induced by insulin (Hollenberg, 1959) and could thus be reduced in some diabetics. Moreover the uptake and re-esterification of the liberated fatty acid by the adipocyte (Robinson, 1965) requires α -glycerophosphate. The latter is derived from the glycolytic pathway which may be deficient in diabetes

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thus contributing to an impairment of triglyceride removal.

Using the intravenous fat tolerance test (Boberg, Carlson, and Hallberg, 1969; Lewis, Boberg, Mancini, and Carlson, 1972a) as a measure of fractional removal rate (K_2) of triglyceride we have shown low removal rates both in diabetics requiring insulin and in those controlled by diet alone (Lewis *et al*, 1972). The K_2 rose, often markedly, on correction of the diabetic state. There was also a highly significant negative correlation between the initial triglyceride levels and the K_2 , ie, those diabetics with the slowest removal rates had the highest lipid levels. This suggests that impaired removal of triglyceride must at least be playing a part in the pathogenesis of the diabetic hyperlipidaemia.

The lipid abnormality is usually corrected by effective treatment of diabetes whatever treatment is used, although often more slowly than the abnormality of glucose metabolism. The view that elevated blood lipid levels may persist in diabetics whose blood glucose is controlled (Hayes, 1972) may therefore be the result of too short a period of observation; alternatively, the criteria taken to indicate satisfactory control of blood glucose may be inadequate. As diabetes is a disorder of both carbohydrate and lipid metabolism both blood glucose and lipid levels should return to normal with anti-diabetic treatment before it can be regarded as adequate. Specific drugs are seldom indicated for the lipid abnormality but clofibrate is useful in the management of exudative diabetic retinopathy.

Alcohol

It has only recently been appreciated that mild to moderate elevation of plasma triglyceride and VLDL is a common accompaniment of excessive alcohol consumption; in contrast, the syndrome of gross lipaemia, jaundice, and haemolytic anaemia occurring after an alcoholic bout, first described by Zieve in 1958, occurs rarely.

The mechanism of the hyperlipidaemia appears to be different from that in diabetes mellitus. In alcoholic hypertriglyceridaemia withdrawing alcohol resulted in a fall in the plasma lipid levels, but the rate of removal from plasma did not change (Chait, Mancini, February, and Lewis, 1972). This is in sharp contrast to the diabetic situation and suggests that the factor leading to the elevated plasma triglyceride levels in alcoholics is increased secretion rather than impaired removal.

A possible explanation for alcohol-induced hypersecretion of triglyceride by the liver has been put forward by Lieber (Lieber and Schmid, 1961; Lieber

and Davidson, 1962) who has shown that alcohol metabolism by the liver utilizes NAD. This could diminish the availability of NAD for the oxidation of fatty acids, accumulation of which would favour enhanced triglyceride formation. This could explain both the fatty liver and hypertriglyceridaemia seen in such patients, but fails to explain why all alcoholics do not become hyperlipidaemic. However, we found a low or low normal K_2 level in most alcoholics with hyperlipidaemia, and, as this did not change with improvement of the hyperlipidaemia, we believe that a slow removal rate (due to genetic or other reasons) predisposes to hypertriglyceridaemia from an alcohol-induced increase in hepatic triglyceride secretion (Chait *et al*, 1972).

Chronic Renal Disease

Hyperlipidaemia has long been familiar in the nephrotic syndrome. Any abnormal lipoprotein pattern may occur. The severity of the hyperlipidaemia appears to be related to the severity of the hypoalbuminaemia, and an early concept was that excessive apolipoprotein formation occurs as part of the generalized increased protein turnover seen in any protein-losing state.

More recently it has been reported that hyperlipidaemia also occurs in non-nephrotic chronic renal failure (Losowsky and Kenward, 1968; Bagdade, Porte, and Bierman, 1968; Brøns, Christensen, and Hørdér, 1972), the increase being nearly always of the major triglyceride-bearing lipoproteins. Recent results from our laboratory suggest that there may be a qualitative abnormality in VLDL in this condition. Of 11 samples from patients with both chronic renal failure and hyperlipidaemia, eight had an increase in VLDL triglyceride content and nine an increase in VLDL cholesterol with a mean VLDL triglyceride/cholesterol ratio of 2.7 (normal 3.3-4.7). Low-protein, high-carbohydrate diets may contribute in some cases, as high carbohydrate intake can induce elevations of serum triglycerides even in normal subjects (Antonis and Bersohn, 1961; Glueck, Levy, and Fredrickson, 1969). Nevertheless, hyperlipidaemia is seen in chronic renal failure even in the absence of such diets, and sometimes persists after regular haemodialysis (Bagdade *et al*, 1968).

Bagdade *et al* (1968) found hyperinsulinaemia in a group of uraemic patients and, as hepatic triglyceride secretion is dependent on insulin, this may contribute to hyperlipidaemia in uraemia. However, several workers have found subnormal postheparin lipolytic activity suggesting that defective removal may also play a part (Bagdade *et al*, 1968; Boyer and Scheig, 1970).

In view of the increasing use of maintenance dialysis and the increased longevity of patients with chronic renal failure, it may become necessary to treat the hyperlipidaemia in its own right if atherosclerosis is not to become the life-shortening factor.

Hypothyroidism

The lipid abnormality in hypothyroidism is due to an increase in normal β -lipoprotein, often with a concomitant elevation of pre- β -lipoprotein (Tulloch, Vydelingum, Lewis, and Fraser, 1972), and is believed to be due to reduced catabolism of β -lipoproteins. Clinical evidence of hypothyroidism can be minimal or even absent, and laboratory investigations are essential before hypothyroidism can be excluded as a cause of hyperlipidaemia. A recent area of interest has been the concept of 'pre-clinical myxoedema'. It has been suggested that thyroid disease may give rise to high serum cholesterol levels not only without clinical evidence of hypothyroidism (Bastenie, Vanhaelst, Bonnyns, Neve, and Staquet, 1971; Fowler, Swale, and Andrews, 1970) but also with normal levels of serum protein-bound iodine and, in some cases, normal radioiodine uptake (Fowler *et al*, 1970). Considerable further work will be required before this entity can be regarded as established.

Gout

The association of gout and hyperlipidaemia is complex. Hyperuricaemia occurs commonly in primary hypertriglyceridaemia and clinical gout may occur. Furthermore, primary gout can lead to a secondary hypertriglyceridaemia. The two conditions may also coexist due to a common cause such as alcoholism, chronic renal failure, myxoedema, glycogen storage disease, or the dysglobulinaemias. Not surprisingly, in an individual patient it can be difficult to assess which of these factors is operative.

In a group of patients with gout, Bluestone, Lewis, and Mervart (1971) found a 20% incidence of hyperlipidaemia which persisted even after correction of the hyperuricaemia.

Other Endocrine Disorders and Oral Contraceptive Medication

Several endocrine diseases listed in the table are sometimes associated with hyperlipidaemia, usually of mild degree. The interest in the oral contraceptive field arose largely from the different incidence of coronary heart disease between males and premenopausal females. Oestrogens were thought to exert a protective effect. However oral contraceptives

have been shown to elevate the plasma triglyceride concentration in most subjects taking them (Hazzard, Spiger, Bagdade, and Bierman, 1969), though often without exceeding the normal range, and the mechanism appears to be one of enhanced secretion (Kekki and Nikkilä, 1971; Rössner, Larrson-Cohn, Carlson, and Boberg, 1971). The oestrogen component appears responsible (Stokes and Wynn, 1971) and the continued widespread use of oestrogen-containing oral contraceptives may reduce the degree of protection against ischaemic heart disease at present enjoyed by premenopausal females.

Obstructive Liver Disease

The hypercholesterolaemia associated with this condition has been found to be due to an abnormal β -lipoprotein called lipoprotein-X (Russ, Raymont, and Barr, 1956). In contrast to normal β -lipoprotein it migrates cathodally on agar gel electrophoresis and can be identified immunologically (Seidel, Alaupovic, and Furman, 1969). It has potential in the laboratory diagnosis of obstructive versus hepatocellular jaundice, although it does not distinguish intrahepatic from extrahepatic obstruction, and may be absent in jaundice due to gallstones.

Conclusion

The secondary hyperlipidaemias, including rarer entities not discussed above, form an important group of patients seen at any lipid disorders clinic, and have accounted for about one-third of all patients seen at the Hammersmith Hospital Lipid Clinic in the past year. Because of the strong association between hyperlipidaemias and atherosclerosis, the incidence of the latter may be reduced in this group by early recognition and appropriate treatment.

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