Lipaemia Retinalis in Untreated Diabetes Mellitus

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Fyfe, W. M., Hall, Margaret S., and Scott, Janet W. (1970). *Archives of Disease in Childhood*, 45, 84 **Lipaemia retinalis in untreated diabetes mellitus.** A 6-year-old girl developed diabetes mellitus, with marked hyperlipaemia and lipaemic retinalis, both of which rapidly cleared after insulin treatment. Biochemical studies led to the conclusion that dietary fat was the chief source of the excess triglyceride in the blood.

When hyperlipidaemia occurs in the untreated or poorly controlled diabetic the serum lipid levels are usually only moderately increased. Occasionally, however, the serum lipid levels are markedly increased, the serum is turbid, and lipaemia retinalis or eruptive xanthomata may be associated findings (Hamwi *et al.*, 1962; Shipp, Wood, and Marble, 1964; Bagdade, Porte, and Bierman, 1967). This lipaemic syndrome usually occurs in insulin-dependent diabetic patients whose diabetes is poorly controlled, who have chronic insulin insufficiency, and who are symptomatic for long periods (Bagdade *et al.*, 1967); it is unusual in a child with untreated diabetes. We describe here a girl of 6 years admitted in diabetic coma who had conspicuous hyperlipaemia and lipaemia retinalis. With control of her diabetes the serum lipid levels gradually returned to normal.

Case Report

A girl born in February 1960 was well until the age of 6 in February 1966, when she had measles. After this illness her appetite increased but despite this she lost weight; in addition she became increasingly listless and developed nocturia. In June 1966, she had tonsillitis treated with penicillin. By the end of June 1966, she was extremely weak, had polydipsia and polyuria, and was constipated. On 3 July 1966, she developed hyperpnoea. In the early morning of 4 July 1966, she had severe abdominal pain, and later that morning she became unconscious.

On admission to hospital on 4 July 1966, she was thin, dehydrated, and in coma. Her temperature was 37.8° C., heart rate 138/minute, respiratory rate 42/minute with hyperpnoea, and blood pressure 90/65 mm. Hg. Her abdomen was distended and tense. The appearance of her ocular fundi was typical of lipaemia

retinalis. No xanthomata were present. Hepatomegaly with the liver edge four fingerbreadths below the costal margin, was detected a few days after admission, when the abdominal distension had decreased sufficiently to permit palpation of the liver edge. The spleen was not palpable.

The serum of the blood sample obtained at the time of her admission to hospital looked like thick cream; analysis gave:—sugar 504 mg./100 ml., urea 56 mg./100 ml., chloride 70 mEq/l., sodium 100 mEq/l., potassium 3.4 mEq/l., triglycerides 11,520 mg./100 ml. (normal 40–125), total cholesterol 1680 mg./100 ml. (normal 125–250), free cholesterol 830 mg./100 ml. (normal 20%–40% of total cholesterol), ester cholesterol 850 mg./100 ml. (normal 60%–80% of total cholesterol), phospholipids 1375 mg./100 ml. (normal 150–275) and free fatty acids 1500 μ mole/l. (normal 230–380).

Paper electrophoresis of this serum and subsequent staining of the strip with Sudan black showed that the normal lipoprotein pattern was replaced by a single broad band extending from the origin to a position in front of the α_2 -globulin.

The serum triglyceride was estimated by the method of Van Handel and Zilversmit (1957). The serum free and ester cholesterol and the serum phospholipids were estimated by methods quoted by Varley (1962). The serum free fatty acids were estimated by the method of Anstall and Trujillo (1965). Paper electrophoresis was carried out according to the method quoted by Smith (1960).

Micro-Astrup analysis of capillary blood obtained at the time of admission gave the following results: pH 7.05, P_{CO_2} 18 mm. Hg, standard bicarbonate 8 mEq/l., base excess minus 23 mEq/l. Glycosuria and ketonuria were present.

She made a satisfactory response to treatment, and good control of her diabetes was established. Her insulin requirement decreased during the first 4 weeks of treatment and from the beginning of August 1966 until the beginning of November 1966 she was maintained on 4 or 6 units insulin zinc suspension (*lente*) daily. During the first 2 weeks of November 1966

Received 2 June 1969.

Calories	1260	1585	1830	1780	2176
Carbohydrate	200g.	220g.	225g.	150g.	200g.
Protein	70g.	75g.	75g.	75g.	92g.
Fat	20g.	20g.	20g.	98g.	112g.
Unsat. fat	—	25g.	50g.	—	—

FIG.—Serum lipid levels during the first 18 weeks of treatment.

her insulin requirement increased to 18 units insulin zinc suspension (lente), and since then has remained at about this level.

The composition of the diets given during the first 18 weeks of treatment and the serum lipid levels during this period are shown in the Fig. During the first week of treatment the only fat in her diet was contained in one pint (600 ml.) or less of skimmed milk, and for the next 26 days her diet contained 20 g. fat. By the end of the first week of treatment the lipæmia retinalis was no longer present. The serum triglycerides were not estimated after the initial measurements until 4 weeks after the start of treatment when the level was within the normal range. After 18 days' treatment the serum cholesterol and phospholipids were still slightly raised, but after 4 weeks' treatment they also had fallen to within the normal range.

With the return of the serum lipid levels to normal the fat content of the diet was increased by the addition of 25 g. and later 50 g. unsaturated fat, using corn oil margarine as the source of this unsaturated fat. The serum cholesterol and phospholipid levels remained normal on these diets, and this led to a trial of diets in which all the fat was animal fat. A diet containing 98 g. fat was given for 2 weeks, and then the fat content was increased to 112 g. for the next 4 weeks. After 2 weeks on the diet containing 112 g. fat the serum cholesterol was 175 mg./100 ml., phospholipids 230 mg./100 ml., and triglycerides 142 mg./100 ml. A high fat diet, therefore, did not cause a recurrence of hyperlipæmia when the diabetes was adequately controlled with insulin therapy. Since mid-November 1966 the fat content of her diet has been about 90 g., and on this diet the serum cholesterol and phospholipids have remained

within the normal range. The serum triglycerides have not been estimated since November 1966.

Family History

There was no family history of diabetes mellitus. Both her parents and her 16-year-old brother were well. Her 11-year-old sister had coeliac disease and also hypertrophy of her left arm and left leg, associated when she was younger with an extensive naevus which had faded. Both parents and her brother and sister had normal serum cholesterol and phospholipid levels (Table). Their serum triglyceride levels were not estimated.

TABLE
Serum Lipids of Family

	Phospho- lipids (mg. P $\times$ 25) (mg./100 ml.)	Cholesterol		
		Total (mg./100 ml.)	Free (mg./100 ml.)	Ester (mg./100 ml.)
Father	280	190	52	138
Mother	195	148	48	100
Brother	200	170	51	119
Sister	230	166	50	116

Discussion

When hyperlipidaemia occurs in the uncontrolled diabetic, most of the lipid which accumulates in the blood is triglyceride. It appears that increased hepatic synthesis of triglyceride, increased dietary

intake of triglyceride, and delayed clearance of triglyceride from the blood may all play a part in causing this hypertriglyceridaemia.

In uncontrolled diabetes increased mobilization of free fatty acids from adipose tissue raises the blood level of free fatty acids, and there is considerable evidence that this promotes increased hepatic synthesis of triglyceride (Steinberg, 1963).

The increased appetite so characteristic of uncontrolled diabetes is likely to lead to an increased intake of fat in the diet.

Delayed clearance of triglyceride from the blood could be caused by low tissue lipoprotein lipase activity, but the evidence about this is conflicting. Subnormal post-heparin lipolytic activity has been found in patients with diabetic hyperlipaemia before insulin therapy (Bagdade *et al.*, 1967) and in insulin-dependent diabetics 48 hours after insulin withdrawal (Bagdade, Porte, and Bierman, 1968), but normal post-heparin lipolytic activity has also been found in diabetic patients with and without hyperlipaemia (Jones, Plotkin, and Arky, 1966). However, in any condition, such as diabetes, in which levels of endogenous triglyceride are raised the clearing of dietary fat is known to be impaired, even though post-heparin lipolytic activity is normal (Fredrickson, Ono, and Davis, 1963; Fredrickson and Lees, 1965).

While both triglyceride synthesized in the liver and dietary triglyceride contribute to the hypertriglyceridaemia the proportion from each of these sources varies. Some untreated diabetics have a marked increase in pre- β -lipoprotein in the plasma (Pantelakis *et al.*, 1964), while others have a marked increase in chylomicrons in the plasma (Salt *et al.*, 1960; Bagdade *et al.*, 1967).

Bagdade *et al.* (1967) showed that in patients with diabetic hyperlipaemia isocaloric substitution of dietary carbohydrate for fat promptly lowered the plasma triglyceride level. Again rats made diabetic with alloxan became hyperlipaemic only if their diets contained fat; on fat-free diets plasma triglyceride levels in control and diabetic rats were virtually identical (Bierman, Amaral, and Belknap, 1966).

In most cases the serum lipid levels return to normal within 48 hours of starting insulin therapy (Hamwi *et al.*, 1962). Pantelakis *et al.* (1964) described a group of diabetic children in whom pre- β -lipoproteinaemia present at the time of diagnosis persisted in spite of insulin therapy, but these workers were uncertain whether such children had an associated idiopathic hyperlipaemia, or whether the persistent accumulation of low density lipoprotein was an integral part of their diabetic state.

In the present case the serum lipid findings indicate that chylomicronaemia was almost certainly present. The relation between cholesterol and phospholipids on the one hand and triglyceride on the other would fit the composition of chylomicrons, and so would the fact that 50% of the cholesterol was unesterified. This suggests that in our patient, as in those described by Bagdade *et al.* (1967), dietary fat was the chief source of the excess triglyceride in the blood. The severity of the hyperlipaemia in the present case can possibly be attributed to a high dietary fat intake during an unusually long symptomatic and presumably insulin-deficient period when clearance of dietary fat from the blood was impaired.

We are grateful to Dr. T. B. Begg and the staff of the MRC unit at the Western Infirmary, Glasgow, for the serum triglyceride estimations and also to Dr. J. W. Chambers for his advice in the management of this patient.

REFERENCES

- Anstall, H. B., and Trujillo, J. M. (1965). Determination of free fatty acids in plasma by a colorimetric procedure: an appraisal of the method and comparison with other technics. *Clinical Chemistry*, **11**, 741.
- Bagdade, J. D., Porte, D., Jr., and Bierman, E. L. (1967). Diabetic lipemia. A form of acquired fat-induced lipemia. *New England Journal of Medicine*, **276**, 427.
- , —, and — (1968). Acute insulin withdrawal and the regulation of plasma triglyceride removal in diabetic subjects. *Diabetes*, **17**, 127.
- Bierman, E. L., Amaral, J. A. P., and Belknap, B. H. (1966). Hyperlipemia and diabetes mellitus. *ibid.*, **15**, 675.
- Fredrickson, D. S., and Lees, R. S. (1965). A system for phenotyping hyperlipoproteinemia. *Circulation*, **31**, 321.
- , Ono, K., and Davis, L. L. (1963). Lipolytic activity of post-heparin plasma in hyperglycemia. *Journal of Lipid Research*, **4**, 24.
- Hamwi, G. J., Garcia, O., Kruger, F. A., Gwinup, G., and Cornwell, D. G. (1962). Hyperlipidemia in uncontrolled diabetes. *Metabolism: Clinical and Experimental*, **11**, 850.
- Jones, D. P., Plotkin, G. R., and Arky, R. A. (1966). Lipoprotein lipase activity in patients with diabetes mellitus, with and without hyperlipemia. *Diabetes*, **15**, 565.
- Pantelakis, S. N., Fosbrooke, A. S., Lloyd, J. K., and Wolff, O. H. (1964). The nature and occurrence of pre-beta-lipoprotein in diabetic children and pregnant women. *ibid.*, **13**, 153.
- Salt, H. B., Wolff, O. H., Nestadt, A., and Lloyd, J. K. (1960). Control of lipaemia in children with diabetes mellitus. The role of insulin and the effects of a diet rich in unsaturated fatty acids. *Lancet*, **1**, 71.
- Shipp, J. C., Wood, F. C., Jr., and Marble, A. (1964). Hyperlipemia following sulfonylurea therapy in young diabetics. *Journal of the American Medical Association*, **188**, 468.
- Smith, I. (1960). *Chromatographic and Electrophoretic Techniques*. Vol. 2. Heinemann, London.
- Steinberg, D. (1963). Fatty acid mobilization: mechanisms of regulation and metabolic consequences. *Biochemical Society Symposia*, **24**, 111.
- Van Handel, E., and Zilversmit, D. B. (1957). Micromethod for the direct determination of serum triglycerides. *Journal of Laboratory and Clinical Medicine*, **50**, 152.
- Varley, H. (1962). *Practical Clinical Biochemistry*. 3rd. ed. Heinemann, London.

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