Hypercholesterolaemia and diabetes mellitus

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SYNOPSIS An association of essential hypercholesterolaemia and diabetes mellitus is postulated. Case records are included to illustrate hypercholesterolaemia secondary to acute diabetes mellitus, and essential hypercholesterolaemia, independent of, but accompanying diabetes mellitus. Whereas in the former the serum cholesterol returns to normal and its attendant clinical manifestations resolve when the diabetes is controlled, this is not so in the latter type.

Evidence is presented to show that impaired carbohydrate tolerance is not a feature of essential hypercholesterolaemia.

Abnormalities of lipid metabolism associated with uncontrolled diabetes mellitus have been assumed to be secondary to the disordered carbohydrate metabolism, an assumption apparently confirmed by the fall in serum cholesterol which usually accompanies control of the diabetes mellitus (Thannhauser, 1950; Haymond and Berry, 1954). Observations on diabetic children in fair or good diabetic control showed that mean serum levels of β lipoproteins and cholesterol were significantly higher in the children with blood sugar levels above 200 mg. per 100 ml. than in those with blood sugars below this figure (Wolff and Salt, 1958).

Failure of an elevated serum cholesterol level to return to normal when diabetic control has been established has been stated to be of serious prognostic importance (Cantarow and Trumper, 1955). The possibility that this continued hypercholesterolaemia may represent an independent metabolic abnormality appears to have received relatively little attention.

The case histories which follow serve to illustrate these two patterns of hypercholesterolaemia which may be encountered in patients with diabetes mellitus.

CASE REPORTS

CASE 1 A woman aged 29 years presented with one year's history of polydipsia, polyuria, lassitude, and weight loss; an augmented appetite may have resulted in a high fat intake.

Examination revealed a cutaneous xanthoma diabeticorum and very striking lipaemia retinalis. Diabetes mellitus was confirmed by the finding of heavy glycosuria with acetonuria, a fasting blood sugar of 205 mg. per 100 ml. rising to 368 mg. per 100 ml. two hours after 100 g. glucose by mouth. The fasting serum was milk

white in appearance and the serum cholesterol 1,458 mg. per 100 ml. Treatment with insulin resulted in a rapid clearance of the xanthomata, lipaemia retinalis, and the plasma lipaemia, the serum cholesterol falling eventually to 166 mg. per 100 ml. (Table I). This patient has been described in greater detail elsewhere (Bloom and Crowley, 1956).

TABLE I
SERUM CHOLESTEROL LEVELS IN CASES 1 AND 2
AFTER STABILIZATION WITH INSULIN

		<i>Serum Cholesterol</i> (mg. per 100 ml.)	
		<i>Case 1</i>	<i>Case 2</i>
Initially		1,458	1,011
After stabilization with insulin		550	—
Days	7	500	—
	10	330	420
	14	350	—
	17	250	—
	21	270	225
	24	300	203
Weeks	28	166	—
	7	—	—
	24	—	—

CASE 2 A youth of 17 years of age was admitted with one month's history of polydipsia, polyuria, weight loss, and weakness.

Examination showed a young man of poor nutrition with clinical dehydration. Ophthalmoscopy revealed striking lipaemia retinalis; there were no skin xanthomata.

Urine analysis showed severe glycosuria and ketonuria; the blood sugar was 350 mg. per 100 ml. The plasma was milk white and the total serum cholesterol 1,011 mg. per 100 ml. Response to insulin was prompt, the diabetic state coming under control within 48 hours; the lipaemia retinalis became rapidly less marked and the retinal vessels were normal again in about 14 days, coincident with the fall in plasma lipaemia and hypercholesterolaemia (Tables I and IA).

TABLE IA
RESPONSE OF PLASMA LIPIDS TO INSULIN THERAPY IN CASE 2

Day of Disease	Neutral Fat (mg./100 ml.)	Cholesterol (mg./100 ml.)	Phospholipids (mg./100 ml.)	Total Lipids (mg./100 ml.)
1	7,858 (0-200)	1,011 (150-300)	1,217 (60-350)	10,095 (570-820)
14	318 (0-200)	420 (150-300)	411 (60-350)	1,149 (570-820)
28	323 (0-200)	225 (150-300)	273 (60-350)	821 (570-820)

In both patients the extreme hyperlipaemia with hypercholesterolaemia which very occasionally accompanies acute diabetes mellitus was well illustrated. Eruptive xanthomata in one and striking lipaemia retinalis in both were the main clinical signs of this metabolic abnormality. Extreme lipaemia was confidently predicted in Case 2 following routine fundus examination on admission.

The clinical signs and hypercholesterolaemia resolved promptly in both patients with control of the diabetes mellitus.

CASE 3 A woman of 65 years, complaining of pruritus vulvae, polydipsia, and polyuria, was referred to hospital for investigation. The patient had well-developed xanthoma palpebrum; there was no evidence of myxoedema, hepatic, or renal disease.

Urinary examination showed heavy glycosuria but no proteinuria. Blood sugar was 198 mg. per 100 ml. fasting and 259 mg. per 100 ml. two hours after ingestion of 50 mg. of glucose. The serum was clear and the serum cholesterol 400 mg. per 100 ml. A low calorie diet failed to control glycosuria, but the patient refused insulin.

Four years later the patient returned complaining of retrosternal pain and at this time an electrocardiogram showed a posterior myocardial infarction. She was then treated with carbutamide which controlled the diabetes initially, but this was not accompanied by a fall in serum cholesterol.

A low fat diet, sitosterol, and finally a 'corn oil' diet were employed in an attempt to reduce the raised serum cholesterol (Fig. 1).

CASE 4 A woman of 59 years was referred to hospital because of retrosternal pain on effort. Examination showed a marked corneal arcus but no other significant abnormality. The electrocardiographic tracing was consistent with a posterior myocardial infarction.

Six months later the patient returned complaining of thirst, polyuria, and pruritus vulvae. Urine analysis showed glycosuria, and the fasting blood sugar was 180 mg. per 100 ml. A glucose tolerance test performed more recently showed a blood sugar of 223 mg. per 100 ml. two hours after ingestion of 5 g. glucose. The serum cholesterol was 530 mg. per 100 ml.; the fasting serum was clear.

Glycosuria was rapidly controlled by a low calorie

FIG. 1

FIG. 2

diet, but control of the diabetes was not accompanied by a fall in the serum cholesterol. A low fat diet, sitosterol, and subsequently a 'corn oil' diet were used in an unsuccessful attempt to reduce the raised serum cholesterol level (Fig. 2).

Both patients demonstrate the association of essential hypercholesterolaemia with diabetes mellitus; in each case levels of serum cholesterol were recorded which were well above those quoted as normal for the sex and age group concerned by Keys, Mickelsen, Miller, Hayes, and Todd (1950). The essential nature of this hypercholesterolaemia was supported by the presence of xanthelasma palpebrum in Case 3, which remained uninfluenced by control of the diabetes, and the presence of a marked corneal arcus in Case 4, which is not a recorded feature of secondary hypercholesterolaemia.

That these cases represented examples of essential hypercholesterolaemia and not hyperlipaemia was supported by the fact that in both the values for neutral fats and phospholipids were normal, and that in neither case was the fasting serum lactescent.

There is little evidence that impairment of carbohydrate metabolism occurs with undue frequency in essential hypercholesterolaemia. During an investigation of families with essential hypercholesterolaemia (Harris-Jones, Jones, and Wells, 1957),

fasting blood sugar estimations were obtained in patients with hypercholesterolaemia and their near relatives. Whereas such fasting blood sugar levels alone cannot exclude impaired carbohydrate metabolism, they remained normal throughout a wide range of serum cholesterol levels (Fig. 3). Glucose tolerance tests, using the standard 50 g. oral method, were performed on six patients with hypercholesterolaemic xanthomatosis, and were found to be

FIG. 3

FIG. 4

normal (Fig. 4). This is in agreement with a similar investigation by Wilkinson, Hand, and Fliegelman (1948).

DISCUSSION

Hypercholesterolaemia accompanying uncontrolled diabetes mellitus is well recognized.

Increased fatty acid metabolism consequent on insulin deficiency results in an increase in concentration of the intermediary products of fat metabolism. Therefore, an increased supply of 'acetate' becomes available for synthesis into keto-acids and cholesterol (Mookerjee and Sadhu, 1957). As would be expected, the abnormal cholesterol metabolism is modified when carbohydrate metabolism is restored towards normal by treatment. This is expressed by the resolution of skin xanthomata, and

rapid fall of the serum cholesterol, which follow stabilization of the diabetes.

Less is known concerning the metabolic defect responsible for essential hypercholesterolaemia. It is an inborn error of metabolism transmitted as an incomplete dominant trait, and detected most commonly in the middle age groups.

Inheritance of two independent metabolic defects may be encountered, as illustrated by the association of diabetes mellitus and gout (Weiss, Segaloff, and Moore, 1957), or hypercholesterolaemia and hyperuricaemia (Harris-Jones, 1957). An association of diabetes mellitus and hypercholesterolaemia would not therefore appear improbable.

In this event one would not expect the clinical manifestation of hypercholesterolaemia, or the serum cholesterol to be necessarily affected by control of the diabetic state. As will be observed in Cases 3 and 4, in which the hypercholesterolaemia was considered to be an essential defect, reduction of the fasting blood sugar was in fact associated with a rise in the serum cholesterol. No valid hypothesis can be offered for this apparent paradoxical behaviour of the serum cholesterol.

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