

PRIMARY TYPE V HYPERLIPOPROTEINAEMIA (MIXED HYPERLIPAEMIA): SUCCESSFUL RESPONSE TO DIETARY RESTRICTION AND SIMFIBRATE

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SYNOPSIS

Primary Type V hyperlipoproteinaemia is quite a rare disorder characterised by an increase in fasting serum pre-beta-lipoproteins and chylomicrons. It often combines the features of both Type I hyperlipoproteinaemia (fat-induced exogenous hyperlipaemia) and Type IV hyperlipoproteinaemia (carbohydrate-induced endogenous hyperlipaemia) and hence the term mixed hyperlipaemia. This paper describes one Chinese male with this disorder who presents with obesity and tuberous xanthomas on both elbows. Laboratory investigations reveal that his fasting serum cholesterol and triglycerides are 434 mg./100 ml. and 1280 mg./100 ml. respectively. The fasting serum kept overnight in refrigerator is found to be turbid with a thin creamy layer floating on top. The diagnosis of Type V disorder is further confirmed by an elevation in pre-beta-lipoproteins and chylomicrons on paper electrophoresis. He is treated with a reducing diet low in fat and carbohydrate as well as with a new hypolipidaemic drug—simfibrate. The result of this combined dietary restriction and simfibrate therapy is most encouraging as there is marked reduction of fasting serum triglyceride and cholesterol levels after twelve weeks.

Hyperlipaemia is one form of hyperlipidaemia characterised by turbid serum as a result of elevated serum triglyceride level. Serum cholesterol level may be normal or elevated. Ahrens *et al*, in 1961 described two forms of hyperlipaemia namely the exogenous fat-induced hyperlipaemia and endogenous carbohydrate-induced hyperlipaemia. However Fredrickson and Lees (1965) were able to distinguish four different forms of hyperlipaemia according to different lipoprotein patterns on paper electrophoresis. It is found that their Type I hyperlipoproteinaemia is similar to exogenous fat-induced hyperlipaemia and their Type IV hyperlipoproteinaemia is similar to endogenous carbohydrate-induced hyperlipaemia, whereas their Type V hyperlipoproteinaemia combines the features of both fat-induced and carbohydrate-induced hyperlipaemia and hence the term mixed hyperlipaemia. In their vast experience with hyperlipidaemic disorders, Fredrickson *et al* (1967) were able only to identify nine patients with Primary Type V Hyperlipoproteinaemia. So far no such disorder was described in Singapore. This paper describes

one Chinese patient with Primary Type V hyperproteinaemia who was successfully treated with combined dietary restriction and simfibrate—a new hypolipidaemic drug.

CASE REPORT

B. M., a 41 year-old Chinese male, was seen in 1972 with two years history of gradually enlarging yellowish nodules over both elbows. He had gained about 20 pounds of weight during the last five years. His past health was good and he denied suffering from severe abdominal pain, gout, renal disease, diabetes mellitus or coronary heart disease. He drank only occasional glasses of beer. None of his relatives had similar cutaneous nodules or suffered from diabetes mellitus, obesity, gout or coronary heart disease.

On clinical examination, the patient was obese and weighed 196 pounds. Tuberous xanthomas with size varying from few millimeters to two centimeters were found over the extensor surfaces of both elbows (Fig. 1). There was no xanthelasma but an incomplete of arcus senilis was noted. Fundoscopic examination showed a normal disc and retina. Clinically the patient had no evidence of chronic liver or cardiovascular disorders. B. P. was 120/80 mmHg. and peripheral pulses were all equally felt. Careful palpation of the abdomen did not reveal any hepatosplenomegaly.

Laboratory investigations showed his fasting blood sugar was 85 mg./100 ml. with a nor-

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Fig. 1. Multiple yellowish tuberous xanthomata over the extensor surface of right elbow.

mal glucose tolerance test. His serum uric acid was 8.6 mg./100 ml. Serum albumin and globulin was 4.5 gm./100 ml. and 3.6 gm./100 ml. respectively. Urine contained no albumin or sugar. Liver function tests were normal. A sample of serum after 12 hours fast was found to contain 1260 mg./100 ml. of triglyceride and 434 mg./100 ml. of cholesterol. The same fasting serum kept overnight at 4°C in the refrigerator was found to be turbid with a thin creamy layer floating on top (Fig. 2). Paper electrophoresis of serum lipoproteins showed an increase in pre-beta-lipoprotein and chylomicrons. E.C.G. was normal.

A diagnosis of Primary Type V hyperlipoproteinaemia with tuberous xanthomas was made at this stage. A family study, though incomplete, was attempted. Clinical examination of his three daughters aged 8, 10 and 12 revealed no cutaneous xanthomas and their fasting serum cholesterol and triglycerides were within normal limits. He was advised to reduce his body weight to an ideal state and took a low calorie diet of 1500 calories which was low in fat and carbohydrate with each contributing to about 1/3 of the total calories. There was only moderate restriction of die-

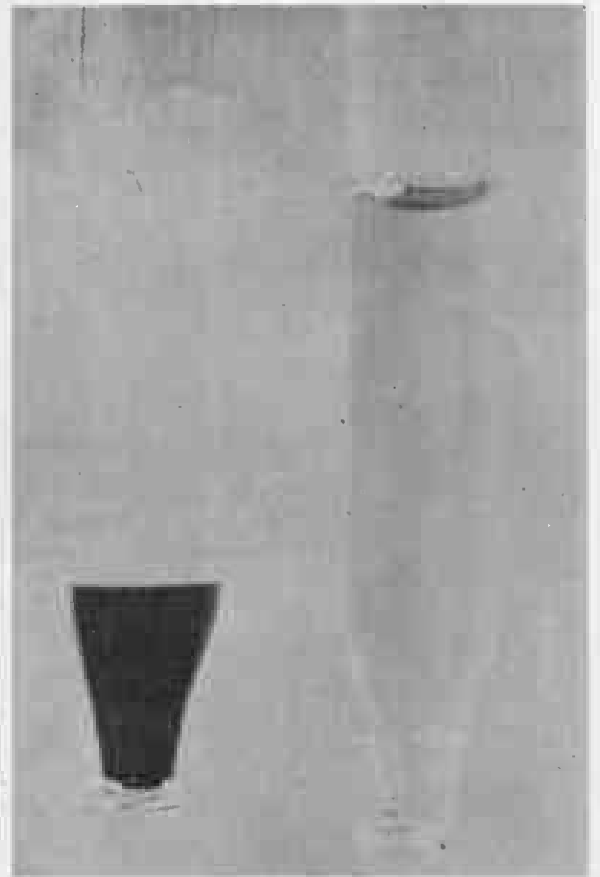


Fig. 2. Fasting serum in test-tube on the left shows uniform turbidity with a thin creamy layer floating on top. Clear serum in the test tube on the right acts as control.

tary cholesterol. As he admitted to his inability to adhere strictly to the dietary restriction, he was started on chemotherapy concurrently without waiting for the dietary therapy to achieve its desired effects. He was started on simfibrate—a new hypolipidaemic drug—in a dose of 500 mg. three times a day. Though his weight reduced only by 4 pounds over the next 2 weeks, the serum triglyceride was reduced by almost 50% from 1260 mg./100 ml. to 702 mg./100 ml., and his serum cholesterol level dropped from 434 mg./100 ml. to 300 mg./100 ml. At the end of 12 weeks, he lost about 10 pounds in weight but his serum cholesterol was back to normal at 200 mg./100 ml. and his serum triglyceride fell further to 214 mg./100 ml. (normal 160 mg./100 ml.) (Fig. 3). The fasting serum kept overnight was found to have lost its turbidity. In addition, the cutaneous xanthomas had reduced in size with disappearance of some smaller nodules. There was no clinical evidence of any adverse reactions to this new drug, simfibrate, and repeated liver function tests, serum electrolytes and blood urea estimations and haematological pictures were all normal.

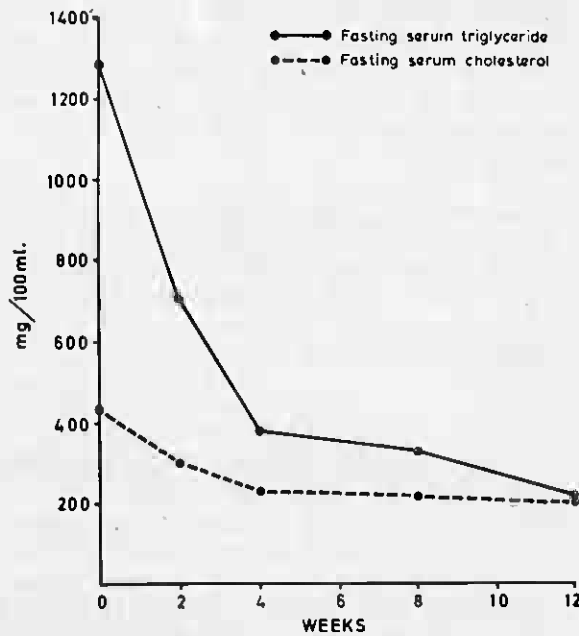


Fig. 3. Reduction in fasting serum triglyceride and cholesterol after treatment with simfibrate and dietary restriction.

DISCUSSION

Type V hyperlipoproteinaemia is characterized by increased amount of pre-beta-lipoprotein and chylomicrons in the fasting serum of patients. Fasting serum triglyceride is elevated which is often more than 1000 mg./100 ml. Serum cholesterol is moderately elevated in this disorder. The appearance of fasting serum kept overnight in the refrigerator is often turbid with a creamy layer floating on top. The turbidity of the serum and the creamy layer is due to increased amount of pre-beta-lipoproteins and chylomicrons respectively.

The clinical features of Type V hyperlipoproteinaemia may mimic those of either Type I or Type IV hyperlipoproteinaemia or it may show both the features of Type I and Type IV. The commonest complaint is the recurrent abdominal pain as in Type I. This has often led to unnecessary exploratory surgery. As in Type I, hepatosplenomegaly and lipaemia retinales may be present. But unlike Type I, which affects only children, Type V affects mainly adults. Though none of the above features described above is found in our patient, he does have cutaneous xanthoma which is commonly present in Type V disorder. It can either be tuberous or eruptive as in Type I and IV disorder. Hyperuricaemia may be present as in this patient. Glucose intolerance is found in 50% of the patients. The patients are often obese and they commonly have family

history of obesity and diabetes mellitus. As with other types of hyperlipoproteinaemia, Type V disorder can either be primary or secondary. Conditions which can give rise to this disorder are nephrotic syndrome, glycogen storage disease, uncontrolled insulin-dependent diabetes mellitus, chronic pancreatitis and alcoholic excess. Primary Type V disorder can occasionally occur as a familial disorder and the pattern of genetic inheritance is most likely autosomal dominance. More than half of the close adult relatives of the patient may have Type V or Type IV disorders.

In Type V disorder, the increase in serum triglyceride is due to triglyceride not only of endogenous origin i.e. the pre-beta-lipoprotein but also of exogenous origin. These patients cannot clear their dietary fat effectively, therefore chylomicrons are present in fasting plasma. When the chylomicronaemia is marked, a clinical picture identical to Type I may develop. The clinical similarity between Type I and Type V has led to the speculation that function of the lipoprotein lipase enzyme system may be impaired in patients with Type V disorder despite normal post-heparin lipolytic activity. Endogenous pre-beta-lipoprotein production may also be so markedly increased as in Type IV that the maximal triglyceride removal capacity of tissues may be exceeded. Therefore the probable mechanism in Type V or mixed hyperlipaemia is diminished clearance of triglyceride-rich lipoproteins that may be present in excess for a variety of reasons.

Though the relationship between Type V disorder and the accelerated atherosclerosis is not very clear, the association between hypertriglyceridaemia and the premature coronary heart disease is more certain. There is no doubt that reduction of triglyceride is desirable. It can also prevent precipitation of pancreatitis and abdominal pain and may lead to disappearance of unsightly cutaneous xanthomas. The management of Type V disorder is complicated by the fact that the hypertriglyceridaemia is secondary to serum chylomicrons and pre-beta-lipoprotein, therefore the physician is denied the easy task of liberal substitution of dietary carbohydrate for fat or vice versa as in the management of Type I and Type IV disorders respectively. It has been found that calories restriction and weight reduction to the ideal state is very effective in reducing the triglyceride-rich lipoproteins. The low calorie diet must also be low in fat and carbohydrate with each contributing to only 1/3 of the total calories (Bricker, 1971). Cholesterol is only moderately restricted. When dietary therapy fails or the patients fail to adhere to the diet, drug therapy may be necessary. Clofibrate 2 gm. per day

may further reduce the triglyceride in some patients (Levy and Fredrickson, 1970). In some other cases, nicotinic acid or progestational hormones are useful (Glueck *et al*, 1969).

A new hypolipidaemic drug, 1-3-propanediol-bis, α -p-chlorophenoxy-isobutyrate (simfibrate), has recently been developed by Yoshitomi Pharmaceutical Industries of Japan. It has a similar structure to ethyl α -p-chlorophenoxy-isobutyrate (clofibrate). It is claimed that the hypocholesterolaemic efficacy of simfibrate is about the same as that of clofibrate but the triglyceride reducing activity of simfibrate is superior (Yoshida *et al*, 1967). Simfibrate at a dose of 1500 mg. per day is given to our patient concurrently with dietary restriction as he is unable to adhere strictly to the diet prescribed. The result of this combined dietary restriction and simfibrate therapy is most encouraging. After two weeks of combined therapy, his weight comes down by four pounds but the fasting triglyceride in the serum drops by about 50% from 1260 mg./100 ml. to 702 mg./100 ml. and the serum cholesterol falls from 434 mg./100 ml. to 300 mg./100 ml. This substantial reduction in serum lipids thus confirms the finding of Yoshida *et al* (1967) that most significant reduction of serum cholesterol and triglyceride occurs during the first two weeks of therapy with simfibrate. At the end of 12 weeks, serum triglyceride drops further to 214 mg./100 ml. though the body weight drops only by 10 pounds from 196 pounds to 186 pounds which is still much higher than his ideal body weight of 162 pounds. It is obvious that

simfibrate combined with dietary restriction is effective in the treatment of Type V hyperlipoproteinaemia and its efficacy in reducing serum cholesterol and triglyceride level is currently being assessed by the authors in other forms of hyperlipoproteinaemia.

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REFERENCES

1. Ahrens, E.H., K. Obette, J.W. Farquhar and Y. Stein: "Carbohydrate-induced and fat-induced lipaemia." *Trans. Ass. Amer. Physns.*, 74, 134, 1961.
2. Bricker, L.A.: "A clinical approach to the hyperlipidemias." *Med. Clin. N. Amer.*, 55, 403, 1971.
3. Fredrickson, D.S. and Lee, R.S.: "A system of phenotyping hyperlipoproteinaemia." *Circulation*, 31, 321, 1965.
4. Fredrickson, D.S., Levy, R.I. and Lees, R.S.: "Fat transport in lipoproteins—an integrated approach to mechanisms and disorders." *New Eng. J. Med.*, 276, 34, 94, 148, 215, 273, 1967.
5. Glueck, C.J., Brown, W.V., Levy, R.I., Greten, H. and Fredrickson, D.S.: "Amelioration of hypertriglyceridaemia by progestational drugs in familial type V hyperlipoproteinaemia." *Lancet*, 1, 1290, 1960.
6. Levy, R.I. and Fredrickson, D.S.: "The current status of hypolipidemic drugs." *Postgrad. Med.*, 47, 130, 1970.
7. Yoshida, S., Fujimoto, J., Tone, K. and Matsumiya, K.: "Clinical experience with CLY-503 (Simfibrate)." *"Shinyo to Shinyaku."* 4, 2071, 1967.