Effects of Insulin and Oral Antidiabetic Agents on the Plasma Triglyceride Levels in Lipoatrophic Diabetes

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SATO, T., SAITO, T., YASUDA, K. and YOSHINAGA, K. Effects of Insulin and Oral Antidiabetic Agents on the Plasma Triglyceride Levels in Lipoatrophic Diabetes. Tohoku J. exp. Med., 1978, 124 (4), 381-385 — Three cases of congenital type of lipoatrophic diabetes were treated with oral antidiabetic agents or insulin for high blood sugar. The plasma triglyceride levels, determined after overnight fasting, were elevated following administration of oral agents or injections of insulin. On these medications, plasma phospholipid and cholesterol also tended to elevate. Paper electrophoresis of plasma revealed an increment of pre-
β-lipoprotein. The levels of plasma triglyceride were reduced when doses of oral antidiabetic agents or insulin were kept constant for several days, and further reduction was observed after withdrawal of these therapeutics. These observations suggest that insulin enhances production and secretion of triglyceride in the liver. ——— insulin; plasma triglyceride levels; lipoatrophic diabetes

In vitro study using the liver slices demonstrated that insulin enhances conversion of glucose to lipids (Salans and Reaven 1966). Perfusion study of the liver also confirmed that insulin promote hepatic triglyceride production (Topping and Mayes 1972). But such insulin action has not been fully demonstrated in man (Bierman 1972), because injections of insulin also cause an increase of plasma triglyceride removal, in part enhancing the activity of lipoprotein lipase (Bagdage et al. 1968).

In lipoatrophic diabetes, impairment of fat storage in the adipose tissue causes characteristic generalized lipodystrophy, hyperlipidemia, and glucose intolerance (Laurence 1946). Reduction of post heparin lipase activity (Torikai et al. 1965), and decrease of removal rate in chylomicron and intrinsic triglyceride were demonstrated in this disorder (Hennes and Sheeve 1959).

The reduced removal rate of plasma triglyceride observed in lipoatrophic diabetes may be regarded as a suitable condition to study the effects of insulin on hepatic triglyceride production. In this study, oral antidiabetic agents or insulin were used to control hyperglycemia in 3 cases of lipoatrophic diabetes. But the treatment did not lower blood sugar and elevated the levels of plasma triglycerides.

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Methods and Subjects

Three subjects of lipoatrophic diabetes, 19, 25 and 34 years old female with total lipodystrophy of congenital type, were studied (Table 1). Glucose intolerance without ketonuria was demonstrated at the age of 14 to 23 years. Hyperlipidemia, hepatomegaly, and muscular hypertrophy were present in all three cases. They were admitted to the hospital and placed on an isocaloric diet.

Case 1 received first administration of chloropropamide, buformin or glybenclamide without effects on blood sugar, and then injection of NPH insulin which was increased gradually from 20 to 90 units per day. Cases 2 and 3 received 250 mg of chloropropamide for about 1 and 3 months, respectively.

The plasma triglyceride levels were determined after overnight fasting using Fletcher's method (Fletcher 1968). Plasma lipoprotein was analyzed by Dr. Maruhama in the Third Department of Internal Medicine of this School of Medicine, using paper electrophoresis.

<table>
<thead>
<tr>
<th>TABLE 1. Clinical data of three cases of lipoatrophic diabetes</th>
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<tr>
<td><strong>Case</strong></td>
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<tr>
<td>Case 1</td>
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<tr>
<td>Case 2</td>
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<tr>
<td>Case 3</td>
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</tbody>
</table>

Results

Case 1 was placed on a 1200 kcal diet which could not control the hyperglycemia, and then administered chloropropamide and glybenclamide followed by insulin injections. But blood sugar was not lowered to normal range by these treatments. Changes of the plasma triglyceride levels in the course of the treatment are shown in Fig. 1. The level of plasma triglyceride were increased after administration of chloropropamide, and returned to normal after stopping it. Readministration of chloropropamide or glybenclamide with and without buformin caused a gradual increase of the plasma triglyceride levels again. NPH insulin was used in 20 up to 90 units per day. In the course of insulin treatment the plasma triglyceride levels were increased to 458 mg/100 ml, and decreased down to 149 mg/100 ml when the insulin dose was kept constant at 52 units per day for 3 weeks. They were elevated again to 659 mg/100 ml when amounts of insulin injected were increased further to 90 units per day, and decreased to 250 mg/100 ml after keeping the dose constant at 90 units per day. Insulin could not lower the blood sugar level, and the insulin injection was discontinued after 6 months, but diabetic state did not become worse. The plasma triglyceride level decreased to as low as 80 to 190 mg/100 ml after withdrawal of insulin injection.

In Case 2, initiation of chloropropamide administration gave rise to the elevation of the plasma levels of triglyceride from 59 mg/100 ml to 249 mg/100 ml, which were reduced to 150 mg/100 ml on the 19th and 75th days after starting chlorpropamide administration. Further reduction of the plasma triglyceride levels down
Fig. 1. Case 1: Changes of plasma triglyceride levels by the treatment with chlorpropamide (C), glybenclamide (G), buformin (B) and NPH insulin.

Fig. 2. Changes of plasma triglyceride levels by the treatment with 250 mg of chlorpropamide (C). Left: Case 2. Right: Case 3.

to 118 and 98 mg/100 ml was observed after withdrawal of chlorpropamide (Fig. 2a).

In accordance with the plasma triglyceride levels, the plasma cholesterol levels were increased to abnormal levels in Case 3. But, compared with plasma phospholipid and cholesterol, the plasma triglyceride levels increased prominently, as shown in Table 2.

Paper electrophoresis of plasma lipoprotein revealed an increase of pre-β-lipoprotein which corresponds to type IV hyperlipoproteinemia of Fredrickson.
TABLE 2. Serum lipids in lipoatrophic diabetes after treatment with insulin or chlorpropamide

<table>
<thead>
<tr>
<th>Case</th>
<th>Triglyceride</th>
<th>Phospholipid (mg/100 ml)</th>
<th>Cholesterol</th>
</tr>
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<tbody>
<tr>
<td>Case 1</td>
<td>695</td>
<td>190</td>
<td>150</td>
</tr>
<tr>
<td>Case 2</td>
<td>249</td>
<td>230</td>
<td>180</td>
</tr>
<tr>
<td>Case 3</td>
<td>2586</td>
<td>520</td>
<td>450</td>
</tr>
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</table>

DISCUSSION

Perfusion study using the liver of animals revealed that insulin enhances hepatic production and release of triglyceride (Topping and Mayes 1972).

In vivo, insulin has effects not only on production but also on removal of plasma triglyceride (Bagdage et al. 1968) and so, effects of insulin on hepatic biosynthesis of triglyceride have not been directly proved in man.

Insulin treatment causes an increase of total plasma lipids in a diabetic (Szaloczky et al. 1975), and also the hyperinsulinemia accounts for the hyperlipidemia (Olefsky et al. 1974). These results suggest that hepatic production and secretion of triglyceride are promoted by insulin.

In lipoatrophic diabetes, removal of plasma triglyceride is impaired (Hennes and Sheeve 1959; Sato et al. 1976), and increased production of triglyceride in the liver by insulin may directly reflect the plasma triglyceride levels.

As shown in this report, administration of oral hypoglycemic agents and injection of insulin caused an elevation of the plasma triglyceride levels, especially at the beginning of administration of oral hypoglycemic agents and when the insulin doses were increased. On the other hand, the plasma triglyceride levels were decreased after discontinuation of the treatment with either oral hypoglycemic agents or insulin.

The increased levels of plasma triglyceride were due to intrinsic triglyceride as evidenced in its migration as pre-β-lipoprotein on paper electrophoresis. Compared with triglyceride, an increment of the plasma cholesterol or phospholipid levels was not so prominent.

As a conclusion, these results indicate that insulin or oral hypoglycemic agents enhance hepatic production and secretion of triglyceride.

References

5) Laurence, R.D. (1946) Lipodystrophy and hepatomegaly with diabetes; lipidemia,


