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# Kinetics of Free Fatty Acids in Hypertriglyceridemia

## Evidence for Different Types of Insulin Resistance<sup>a</sup>

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The plasma free fatty acid (FFA) concentration is elevated in type 2 diabetes mellitus, obesity, and hypertriglyceridemia.<sup>1-3</sup> The magnitude of this abnormality is correlated with the degree of resistance to insulin-stimulated glucose uptake. Plasma levels of FFA reflect the lipolytic activity within adipocytes, activity of lipoprotein lipase, and the uptake and reesterification of FFA. These processes are affected by insulin and other hormones.<sup>4</sup> In contrast to FFA, glycerol released by lipolysis in adipose tissue cannot be reesterified, and it is this difference that makes its release a marker for *in vitro* studies of adipocyte lipolytic activity. It is utilized in the liver. We investigated the possibility of using the measurement of FFA and glycerol kinetics during the frequently sampled intravenous glucose tolerance test (FSIGT) to demonstrate differences between hypertriglyceridemic diabetic subjects, hypertriglyceridemic nondiabetic subjects, and healthy persons.

## METHODS

We examined three groups of age- and weight-matched male subjects: eight healthy volunteers (C), seven hypertriglyceridemic (TG) patients with normal glucose tolerance, and seven well-controlled (on diet only) type 2 diabetic subjects with hypertriglyceridemia (TG-DM). The clinical characteristics are shown in TABLE 1. We measured FFA<sup>5</sup> and glycerol<sup>6</sup> kinetics during the FSIGT. The results were evaluated using Bergman's minimal modeling technique.<sup>7</sup> We computed the half-life of FFA disappearance ( $t_{1/2}$ ) and an "index of insulin-dependent decrease of FFA."<sup>8</sup> We measured glucagon, growth hormone, cortisol (radioimmunoassays), catecholamines (HPLC), and triglycerides before and after the glucose load.

## RESULTS AND DISCUSSION

Results are shown in TABLE 1 and FIGURE 1. No differences in age or body mass index were noted between groups. Fasting plasma concentrations of FFA and

<sup>a</sup>This study was supported by Czech Ministry of Health Grant IGA 0008-2.

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glycerol were increased in the TG-DM group and were much higher again in the TG group. The percentage of FFA and glycerol decrease was similar in the C and TG groups (36 and 42% of basal values). The decrease in the TG-DM group was different (52% of basal values,  $p < 0.05$ ). The values of FFA disappearance half-time ( $t_{1/2}$ ) were also higher in TG-DM group ( $p < 0.02$ ). On the other hand, the absolute decrease in both variables was similar in the C and TG-DM groups and was greater in the TG group ( $p < 0.001$ ). The situation is also complicated by the fact that the TG and TG-DM groups were hyperinsulinemic. Fasting insulin and the area under the insulin response curve after glucose load (TABLE 1 shows the sum of the first 90 minutes of the test) were greater in the TG and TG-DM groups. When we expressed the fall in FFA as the ratio of the relative change in FFA and the sum of the insulin response, we obtained a formal index ( $S_I$ -FFA, "index of insulin-dependent FFA decrease"). Despite the fact that this index was significantly lower in TG and TG-DM groups than in controls, we can only speculate about differences in insulin action in hypertriglyceridemia. The similar decrease in FFA and glycerol suggested that observed changes could reflect mainly the antilipolytic activity of insulin. We have found no significant changes in counterregulatory hormones between the groups and during the FSIGT. Plasma levels of TG were stable during the 180 minutes of the FSIGT. Insulin sensitivity indexes for glucose uptake and for FFA disappearance were correlated ( $r = 0.66$ ,  $p < 0.05$ ) among hypertriglyceridemic patients. Inhibition of lipolysis is probably dominant, but small differences between the kinetics of FFA and glycerol also suggest other mechanisms (e.g., different clearance of FFA and glycerol, release and activation of lipoproteinlipase,<sup>4</sup> and intrinsic overactivity of lipolysis).

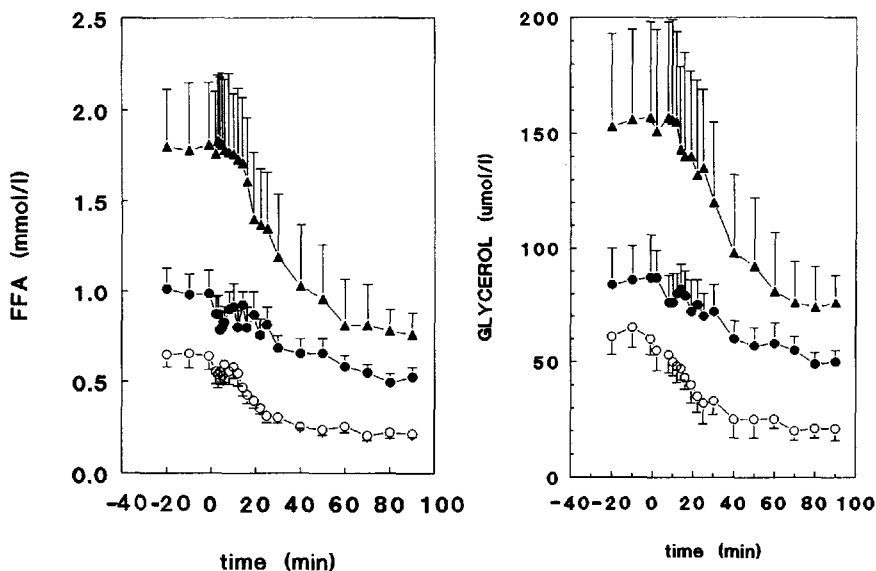
In conclusion, our data, obtained during the FSIGT, are consistent with previous reports showing that insulin regulation of FFA and glycerol is not normal in patients with type 2 diabetes. Our data suggest that a similar situation can be observed in hypertriglyceridemic patients without diabetes mellitus and that the degree of this

TABLE 1. Characteristics of Control Subjects (C), Patients with Hypertriglyceridemia and Normal Glucose Tolerance (TG), and Type 2 Diabetic Subjects with Hypertriglyceridemia (TG-DM) (mean  $\pm$  SD)

Group	C (n = 8)	TG (n = 7)	TG-DM (n = 7)
Age (yr)	43.6 $\pm$ 5.9	45.0 $\pm$ 2.7	46.7 $\pm$ 5.5
Body mass index (kg/m <sup>2</sup> )	24.7 $\pm$ 2.8	26.2 $\pm$ 1.4	25.2 $\pm$ 3.2
TG (mmol/L)	1.21 $\pm$ 0.42	3.04 $\pm$ 0.76 <sup>c</sup>	3.48 $\pm$ 1.16 <sup>c</sup>
Glycohemoglobin (%)	5.31 $\pm$ 0.51	5.23 $\pm$ 0.46	7.16 $\pm$ 2.52
Fasting glycemia (mmol/L)	5.03 $\pm$ 0.36	4.46 $\pm$ 0.38	7.37 $\pm$ 1.35 <sup>c</sup>
Fasting insulin (mU/L)	10.2 $\pm$ 2.6	17.8 $\pm$ 8.9 <sup>a</sup>	28.6 $\pm$ 9.7 <sup>c</sup>
Sum of insulin in FSIGT (min $\cdot$ mU/L)	2903 $\pm$ 303	5736 $\pm$ 1625 <sup>c</sup>	5138 $\pm$ 1718 <sup>b</sup>
Fasting FFA (mmol/L)	0.66 $\pm$ 0.19	1.78 $\pm$ 0.98 <sup>b</sup>	1.03 $\pm$ 0.31 <sup>b</sup>
Fasting glycerol ( $\mu$ mol/L)	61.2 $\pm$ 25.1	152.2 $\pm$ 102.3 <sup>a</sup>	83.4 $\pm$ 47.3
Insulin sensitivity index ( $S_I$ -glucose) (10 <sup>4</sup> $\cdot$ L $\cdot$ min <sup>-1</sup> $\cdot$ mU <sup>-1</sup> )	6.92 $\pm$ 1.64	3.37 $\pm$ 1.15 <sup>c</sup>	2.72 $\pm$ 0.88 <sup>c</sup>
$t_{1/2}$ -FFA (min)	42.3 $\pm$ 18.4	50.9 $\pm$ 17.9	121.1 $\pm$ 72.5 <sup>b</sup>
$S_I$ -FFA (mU <sup>-1</sup> )	2.00 $\pm$ 0.35	1.13 $\pm$ 0.75 <sup>b</sup>	0.79 $\pm$ 0.39 <sup>c</sup>

Significances: 1. versus C: (a)  $p < 0.05$ ; (b)  $p < 0.02$ ; (c)  $p < 0.001$ .

2. TG versus TG-DM: (d)  $p < 0.05$



**FIGURE 1.** Plasma free fatty acids (*left panel*) and glycerol (*right panel*) given as the mean  $\pm$  SEM before and after intravenous glucose ( $t = 0$  minutes,  $0.33 \text{ g/kg}$ ) in eight healthy control subjects ( $\circ\text{--}\circ\text{--}\circ$ ), seven nondiabetic patients with hypertriglyceridemia ( $\blacktriangle\text{--}\blacktriangle\text{--}\blacktriangle$ , *upper curves*), and eight type 2 diabetic subjects with hypertriglyceridemia ( $\bullet\text{--}\bullet\text{--}\bullet$ ). Arterialized venous blood samples (*heated box*) were taken.

alteration is correlated with the degree of resistance to insulin-stimulated glucose uptake.

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