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Glucose-stimulated insulin response in non-diabetic patients with lipoprotein lipase deficiency and hypertriglyceridemia

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Abstract

Elevations in plasma triglyceride (TG) and free fatty acid (FFA) concentrations are generally thought to play a role in the pathogenesis of insulin-resistant diabetes. The objective of this study was to investigate the relationship between hypertriglyceridemia and glucose-stimulated insulin responsiveness in non-diabetic patients. Forty subjects were divided into three BMI-matched groups as follows: one group consisted of 8 patients with a lipoprotein lipase (LPL) deficiency, another consisted of 12 patients with hypertriglyceridemia and a third consisted of 20 subjects with normal TG levels. In response to a 75 g oral glucose tolerance test, plasma insulin levels in the LPL-deficient subjects were higher (106 ± 11 μU/ml) than those in the hypertriglyceridemic (69 ± 16 μU/ml) and normolipidemic (29 ± 3 μU/ml) subjects, at 30 min. On the other hand, their plasma glucose levels (127 ± 6 mg/dl) were less than those seen in the normolipidemic group (165 ± 9 mg/dl) after 90 min.

Thus, LPL-deficient subjects with hypertriglyceridemia displayed an enhanced glucose-stimulated insulin response as well as lower blood glucose levels, the latter of which is not generally seen in those with hypertriglyceridemia and normolipidemia.

Keywords: lipoprotein lipase deficiency; Impaired glucose tolerance; Insulin secretion; Hypertriglyceridemia

1. Introduction

Raised plasma triglyceride (TG) and free fatty acid (FFA) concentrations are thought to play a role in the pathogenesis of insulin-resistant diabetes [1–3]. Elevated plasma FFA levels are thought to contribute to the development of insulin resistance by inhibiting both glucose oxidation and glycogen synthesis [3] in skeletal muscle, and by stimulating glyconeogenesis in the liver [4]. A relationship between glucose and FFA metabolism was reported back by Randle et al. [3], who postulated the existence of substrate competition between FFA and glucose, resulting in the inhibition of glucose uptake and oxidation by increased FFA oxidation. This phenomenon has helped to explain why insulin resistance occurs in patients with non-insulin-dependent diabetes mellitus (NIDDM). Sane

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and Taskinen [1] followed 47 patients with endogenous hypertriglyceridemia for 10 years and concluded that hypertriglyceridemia was a risk factor for the development of type 2 diabetes.

Type 2 diabetics often exhibit increased TG and FFA levels [5,6]. The fasting plasma FFA concentrations in diabetic Pima Indians were reported to correlate with the magnitude of their hyperglycemia and endogenous glucose production [7]. However, whether hyperlipidemia causes diabetes or develops as a result of this disease is unclear. In our study, we examined the glucose-stimulated insulin response in non-diabetic patients with an LPL-deficiency (LPL-def) and hypertriglyceridemia and discussed our results in light of the data reported in an animal model of LPL-def [8].

2. Subjects and methods

Out-patients at our hospital were subjected to a standard oral glucose tolerance test (OGTT; 75 g of glucose), with blood samples drawn at 0, 30, 60, 90 and 120 min after glucose loading. The OGTT data were analyzed using both World Health Organization [9] and American Diabetes Association [10] methods. Normal glucose tolerance (NGT) was defined as a FPG level of <110 mg/dl and a 2-h plasma glucose of <140 mg/dl. Impaired fasting glucose (IFG) was defined as a FPG level of between 110 and 125 mg/dl and a 2-h plasma glucose level of <140 mg/dl. Impaired glucose tolerance (IGT) was defined as a FPG of <110 mg/dl and a 2-h plasma glucose level of between 140 and 200 mg/dl.

Subjects who had been diagnosed with diabetes (FPG > 126 mg/dl and/or a 2-h plasma glucose of >200 mg/dl) or who had already been treated for diabetes were excluded from this study. Hypertriglyceridemia was defined by a fasting plasma triglyceride level of over 150 mg/dl.

Eight patients diagnosed with LPL-def, based on their plasma immuno-reactive LPL levels (ng/ml) before and after the administration of intravenous heparin-sulfate (30 unit/kg weight) [11], were subjected to oral glucose tolerance testing; five of these subjects had NGT, one had IFG and two had IGT, and their mean ± S.E. BMI was 25.9 ± 1.4 kg/m^2. Their results were compared to those obtained from 32 BMI-matched patients with an LPL-def, 12 of whom had hypertriglyceridemia (high-TG; six with NGT, two with IFG and four with IGT, BMI 27.3 ± 1.1) and 20 who had normal TG levels (norm-TG; eight with NGT, three with IFG, eight with IGT and one with IFG/IGT, BMI 24.9 ± 0.6). None of these 32 patients had an LPL-def.

In the above LPL-def patients, LPL protein mass was determined using a Markit-F LPL EIA Kit (Dainippon Pharmaceutical Co., Ltd., Osaka, Japan). Values under 150 ng/ml were indicative of heterozygous LPL-def (normal range 146–286 ng/ml) [11,12]. Hepatic TG lipase (HTGL) mass was determined as previously reported (normal range in males and females = 920–2858 and 632–1818 ng/ml, respectively) [11]. Three LPL-def patients were found to have a genetic disorder as determined by polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP) analysis and by gene sequence analysis [13]. Finally, one of these patients had been diagnosed at our hospital with homozygous LPL-def; her LPL activity and heparin response were almost zero (Table 1). A homozygous substitution of TGA/Trp382 (stop codon) for TGG1404 was identified in this individual based on LPL gene sequence analysis [14].

OGTTs (75 g of glucose) were performed in the above patients, the results of which were evaluated by calculating the $\sum PG_{0-120}$ and $\sum IRI_{0-120}$ (sum of the values of plasma glucose (PG) or IRI time from 0 to 120 min) [15]; the patients' HOMA-R and insulinogenic index (I.I.) were also calculated.

The patient with the homozygous LPL-def was followed for 17 years, over which time his glucose and IRI responses were analyzed. Specifically, euglycemic hyperinsulinemic glucose clamp measurements [16] and glucose infusion rate calculations were determined (GIR; mg/(kg min)) in order to quantify the patient's degree of insulin resistance. The data obtained from this patient were compared to those obtained from our two obese patients with hypertriglyceridemia.

Table 1
Clinical characteristics and lipid profile of our patients with LPL-deficiency

Patient	Age	Sex	BMI	TC (mg/dl)	TG (mg/dl)	HDL-C (mg/dl)	FFA (mEq/l)	ALPL (ng/ml)	AHTGL (ng/ml)	Diagnosis
TI	40	F	22.0	168	1006	18.0	0.60	0	2218	LPL-def (homo)[a]
NF	42	M	21.7	203	561	40.2	0.56	145	2100	LPL-def (hetero)
TA	30	F	23.3	222	718	34.9	0.53	79	945	LPL-def (hetero)
AS	20	F	24.8	189	353	28.8	0.25	122	273	LPL-def (hetero)
KW	30	F	30.0	258	554	35.7	0.88	203	360	LPL-def (hetero)[a]
SN	61	F	25.9	222	537	33.5	–	133	–	LPL-def (hetero)
ST	31	M	26.8	183	583	37.0	0.72	87	2458	LPL-def (hetero)
TT	57	F	33.3	235	554	44.2	0.88	203	360	LPL-def (hetero)[a]
Mean (±S.E.)			25.9 (1.4)	210.0 (10)	608 (66)	34.0 (2.7)	0.63 (0.08)	121 (23)	1244 (370)	

[a] These patients were identified and characterized as having a genetic disorder by PCR-SSCR and gene sequence analysis.