α-Lipoic Acid Treatment Decreases Serum Lactate and Pyruvate Concentrations and Improves Glucose Effectiveness in Lean and Obese Patients With Type 2 Diabetes

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OBJECTIVE — We examined the effect of lipoic acid (LA), a cofactor of the pyruvate dehydrogenase complex (PDH), on insulin sensitivity (S_I) and glucose effectiveness (S_G) and on serum lactate and pyruvate levels after oral glucose tolerance tests (OGTTs) and modified frequently sampled intravenous glucose tolerance tests (FSIGTTs) in lean ($n = 10$) and obese ($n = 10$) patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — FSIGTT data were analyzed by minimal modeling technique to determine S_I and S_G before and after oral treatment (600 mg, twice a day, for 4 weeks). Serum lactate and pyruvate levels of diabetic patients after glucose loading were compared with those of lean ($n = 10$) and obese ($n = 10$) healthy control subjects in which S_I and S_G were also determined from FSIGTT data.

RESULTS — Fasting lactate and pyruvate levels were significantly increased in patients with type 2 diabetes. These metabolites did not exceed elevated fasting concentrations after glucose loading in lean patients with type 2 diabetes. However, a twofold increase of lactate and pyruvate levels was measured in obese diabetic patients. LA treatment was associated with increased S_G in both diabetic groups (lean 1.28 ± 0.14 to 1.93 ± 0.13; obese 1.07 ± 0.11 to $1.53 \pm 0.08 \times 10^{-2}$ min^{-1}, $P < 0.05$). Higher S_I and lower fasting glucose were measured in lean diabetic patients only ($P < 0.05$). Lactate and pyruvate before and after glucose loading were ~45% lower in lean and obese diabetic patients after LA treatment.

CONCLUSIONS — Treatment of lean and obese diabetic patients with LA prevents hyperglycemia-induced increments of serum lactate and pyruvate levels and increases S_G.

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Abbreviations: AUC, area under the curve; FSIGTT, modified frequently sampled intravenous glucose tolerance test; LA, α-lipoic acid; MII, mean incremental insulin; OGTT, oral glucose tolerance test; PDH, pyruvate-dehydrogenase; S_I, insulin sensitivity; S_G, glucose effectiveness.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Experimental data have revealed some beneficial effect of α-lipoic acid (LA, also known as thioctic acid), a potent lipophilic free radical scavenger (1), on glucose metabolism by enhancing glucose uptake in muscle cells (2–4) and by preventing glucose-induced protein modifications (5). Furthermore, LA reduced serum lactate and pyruvate concentrations by stimulating directly pyruvate-dehydrogenase (PDH) activity in diabetic rats (6). Clinical studies with the hyperinsulinemic-isoglycemic glucose clamp showed a significant improvement of insulin sensitivity (S_I) in patients with type 2 diabetes after intravenous application of lipoic acid (7,8). However, the exact mode of action of this vitamin-like substance remains to be elucidated.

LA is a cofactor in the multienzyme complexes of PDH, α-ketoglutarate, and branched chain α-ketoacid dehydrogenases, which seem to be impaired in patients with type 2 diabetes (9). Various experimental data describe a reduced PDH activity in muscle and fat tissue (10,11) in humans; however, the data available in this context are not entirely consistent. Under basal conditions and during euglycemic clamp studies, increased glucose oxidation and PDH activity have been found in skeletal muscle (12,13). However, Thorburn et al. (14) could show that a defect in glucose oxidation exists that cannot be overcome by increasing insulin concentrations and cannot be explained by obesity, impaired fat oxidation, and reduced glucose uptake (15). They suggested that the likely cause for the diminished glucose oxidation would be a defect located at the mitochondrial PDH in patients with type 2 diabetes. Recently, Avogaro et al. (16) demonstrated that intracellular lactate and pyruvate interconversion rates are greatly enhanced in muscle of obese patients with type 2 diabetes in the postabsorptive state, suggesting that lactate/pyruvate metabolism is impaired in patients with type 2 diabetes. The oxidation of glucose after a 100-g

Table 1—*Characteristics of control and diabetic subjects*

	Control subjects		Type 2 diabetic subjects	
	Lean	Obese	Lean	Obese
n	10	10	10	10
Age (years)	53.5 ± 6	51.7 ± 7	56.2 ± 1.7	51.5 ± 4
BMI (kg/m²)	23.8 ± 0.9	29.5 ± 0.3†	23.6 ± 0.50	29.09 ± 0.7§
HbA_{1c} (%)	4.4 ± 0.2	4.6 ± 0.3	6.5 ± 0.2	8.1 ± 0.2§
Fasting glucose (mmol/l)	4.5 ± 0.1	4.8 ± 0.3†	9.04 ± 0.40#	11.70 ± 0.61¶ ††
Fasting insulin (pmol/l)	44.0 ± 3	78.3 ± 5†	48.8 ± 4.7	68.1 ± 4.6§
Fasting lactate (mmol/l)	1.78 ± 0.20	2.26 ± 0.21	2.42 ± 0.17**	2.76 ± 0.12‡‡
Fasting pyruvate (μmol/l)	60.7 ± 3.4	87.2 ± 6.6†	90.99 ± 6.1#	128.87 ± 8.9‡ ‡‡
Triglyceride (mg/dl)	132.8 ± 18	268.3 ± 21†	153 ± 8	334 ± 12§
Diabetes duration (years)			7.3 ± 1.0	5.8 ± 0.7
MII from OGTT (pmol/l)	309.98 ± 3.20	787.14 ± 91.02	230.41 ± 11.5	207.68 ± 28.48

Data are means ± SEM. *$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$ obese versus lean control subjects; §$P < 0.01$, ¶$P < 0.001$ obese versus lean type 2 diabetic subjects; #$P < 0.001$, **$P < 0.01$ lean type 2 diabetic subjects versus lean control subjects; ††$P < 0.0001$, ‡‡$P < 0.01$ obese type 2 diabetic subjects versus obese control subjects.

oral glucose tolerance test (OGTT) is decreased from 40% in control subjects to 27% in patients with type 2 diabetes (17). Thus, we suggest that increasing serum pyruvate levels during OGTT could be derived from a defect in PDH activity resulting in an impaired glucose oxidation in patients with type 2 diabetes (18,19).

The intravenous glucose tolerance test as standard or modified frequently sampled intravenous tolerance test (FSIGTT) with insulin interpreted with the minimal model of glucose disappearance is a powerful noninvasive tool with which to investigate glucose metabolism in physiopathology studies. The model provides two metabolic indexes measuring glucose effectiveness (S_G) and insulin sensitivity (S_I) in a single individual. S_G and S_I are composite parameters, that is, they measure the net effect of glucose and insulin, respectively, to promote glucose disappearance and inhibit endogenous glucose production. Because of the severe insulin resistance and the reduced insulin secretion in type 2 diabetes, glucose effectiveness represents the predominant factor regulating glucose uptake in these patients.

First, using a minimal modeling analysis of FSIGTT data, we tried to find out whether the oral application of LA is able to improve insulin sensitivity in lean and obese patients with type 2 diabetes. Second, because glucose effectiveness is also reduced in patients with type 2 diabetes (20,21), we evaluated the influence of LA on S_G in these patients. Third, we measured serum lactate and pyruvate concentrations after OGTTs and FSIGTTs in lean and obese control subjects as well as in lean and obese patients with type 2 diabetes to test the hypothesis that insufficient PDH activity is characterized not only by increasing serum lactate, but above all, by increasing pyruvate concentrations and may differ in nondiabetic and diabetic subjects. Finally, we tried to find out whether in the case of elevated serum pyruvate levels, the cofactor of the PDH complex, α-lipoic acid, is able to improve the glucose disposal rate in these patients by accelerating pyruvate metabolism.

RESEARCH DESIGN AND METHODS

Subjects

OGTT and modified FSIGTT were performed in lean ($n = 10$) and obese ($n = 10$) healthy subjects and in male lean ($n = 10$) and obese ($n = 10$) patients with type 2 diabetes. All obese subjects had a BMI >25 kg/m². All subjects undergoing these tests were men. The characteristics of the subjects are given in Table 1. Exclusion criteria were positive family history of diabetes for control subjects, malignancies, hepatic or renal disease (normal creatinine clearance without albuminuria), and age >65 years for control subjects and diabetic subjects. OGTT and modified FSIGTT were repeated in lean and obese patients with type 2 diabetes 4 weeks after oral treatment with LA (600 mg, twice a day, one dosage in the morning; the other in the evening with a time interval of 12 h) (ASTA-Medica, Frankfurt, Germany). Since first-pass effect of LA by the liver is ~30% (product information, ASTA Medica) and studies with different parenteral doses have shown that metabolic effects are evident in doses over 500 mg LA (8), we used an oral dose of 1,200 mg per day.

Oral hypoglycemic agents (lean diabetic patients, $n = 2$, metformine 500 mg twice a day; obese diabetic patients, $n = 4$, metformine 500 mg three times a day) were withdrawn at least 2 weeks before the tests were performed. No other hypoglycemic drug was given during the 4 weeks of LA treatment. All diabetic subjects performed self-control measurements of blood glucose three times a day. The tests were performed at least 3 days apart. The study was approved by the local ethics committee. Informed consent was given from control subjects and diabetic patients.

OGTT

Subjects were given 75-g of glucose orally in the morning after a 10- to 12-h overnight fast. No medication was taken by the patients before the tests started. Blood samples were obtained without tourniquet from the antecubital vein before and 30, 60, 90, and 120 min after glucose load for the analysis of glucose, insulin, pyruvate, lactate, and 3-β-hydroxybutyrate. Before starting the therapy and after 4 weeks during treatment with LA, triglyceride concentrations and HbA_{1c} were determined.

Modified FSIGTT

After overnight fasting, a polyethylene catheter was inserted in the antecubital vein for blood sampling. Another catheter was placed in the contralateral arm for intravenous glucose and insulin administration. Baseline samples for insulin and glucose were obtained at −15, −10, −5, and 0 min. Sampling protocol for measurement of glucose and insulin concentrations was used as described (22). Glucose (300 mg/kg body wt, 50% solution) was administered intravenously within 2 min (23), and 0.05 U/kg insulin in diabetic patients and 0.02 U/kg body wt in control subjects was injected as a bolus at time 20 as previously described (24). Samples for the assays of serum pyruvate, lactate, and 3-β-hydroxybutyrate concentrations were collected at 0, 10, 20, 30, 60, 120, and 180 min.

Analytical methods

Plasma glucose concentration was measured in duplicate by the glucose oxidase method using a glucose analyzer (Beck-

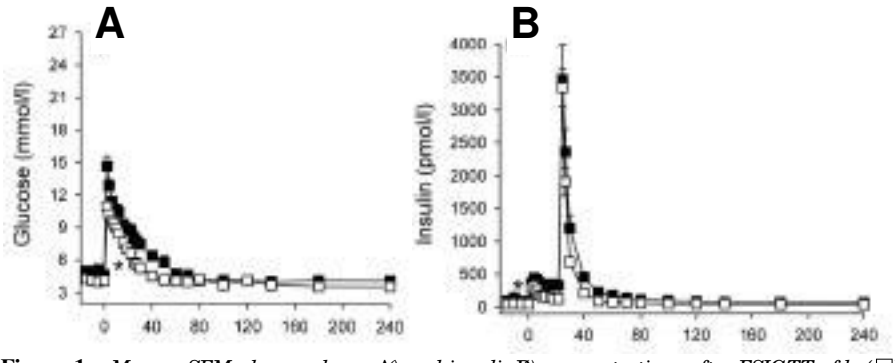

Figure 1—*Mean ± SEM plasma glucose (A) and insulin (B) concentrations after FSIGTT of lean (□) and obese (■) control subjects (fasting glucose and insulin were significantly higher in obese control subjects, *P < 0.01).*

mann Clinical System 700). Blood samples for plasma insulin were immediately centrifuged at 4°C and stored at −20°C until analysis. Insulin concentrations were measured by Microparticle-Enzyme Immunoassay (MEIA Insulin, IMX System, Abbott, Germany). Within the assay, the coefficient of variation was 5.3%; total assay variation was 6.2%. Blood samples for pyruvate (coefficient of variation, 6.1%) were immediately deproteinized with cold perchloric acid (4°C) and then centrifuged and measured using a standard commercial kit (MPR 1 Pyruvat 124982, Boehringer Mannheim, Germany). Lactate (coefficient of variation, 5.3%) and β-hydroxybutyrate were determined by enzymatic fluormetric assays (MPR 3 Test, Boehringer Mannheim, Germany). HbA_{1c} was measured by high-performance liquid chromatography (HPLC). Triglycerides were measured enzymatically (TG, SYS 3; Boehringer Mannheim, Mannheim, Germany).

Data analysis

Data analysis of the FSIGTT was performed after completing the study. The investigator performing the data analysis was unaware of the group distribution. FSIGTT data analysis was based on the Bergman et al. (25) minimal model of glucose disappearance. The minimal model is a linear, time-varying model of glucose disappearance often used to investigate glucose metabolism in vivo in physiopathological studies from standard or modified intravenous glucose tolerance tests. The model is used to fit the plasma glucose time course while assuming that the time course of insulin is known, and in the process, provides two metabolic indexes that measure S_G and S_I. It must be appreciated that these parameters are composite parameters; that is, they measure the effect of glucose and insulin, respectively, both to enhance the glucose disappearance rate and to inhibit endogenous glucose release (i.e., they cannot segregate the contribution of the liver and the peripheral tissue to plasma glucose kinetics). Glucose and insulin profiles were analyzed using SAAM II software, version 1.0.2 (University of Washington, Seattle, WA). Weights for the weighted least-squares optimization were chosen equal to the inverse of the variance of glucose measurement error, determined to be Gaussian, zero mean and with an SD equal to 2% of the measured glucose value. To mitigate the consequences of the single-compartment approximation of glucose kinetics on which the minimal model relies, glucose data points up to 8 min were neglected during the fitting process. Basal end test glucose and insulin concentrations, necessary for the minimal model identification, were calculated as the mean of the last three data points. Precision of parameter estimates was expressed as fractional SD (FSD, the ratio between the SD of the estimate and the estimated value, expressed as percent).

The mean incremental plasma insulin concentration (MII) during the OGTT was calculated as the incremental area under the plasma curve (using the trapezoidal method) divided by 180 min. The area under the curve (AUC) was calculated for the serum lactate and pyruvate increments after FSIGTT.

Statistical analysis

Data are expressed as means ± SEM. To evaluate the differences between the control groups, data were analyzed by Student's *t* test or the rank-sum test if normality test failed. S_I and S_G data of patients with type 2 diabetes before and after treatment were compared with paired Student's *t* test or Wilcoxon's signed-rank test if normality failed. To evaluate differences between controls and patients with type 2 diabetes, data were analyzed by one-way analysis of variance (ANOVA). Correlations were determined using linear regression; a *P* value of <0.05 was considered significant.

RESULTS

Metabolic parameters of controls and patients with type 2 diabetes in the fasting state

Fasting glucose, insulin, and triglycerides concentrations were significantly different in lean and obese control subjects (Table 1). Fasting lactate concentrations were not different between both control groups ($P = 0.06$); however, pyruvate levels were significantly increased in obese control subjects (Table 1).

Lean patients with type 2 diabetes had lower HbA_{1c}, fasting glucose, lactate, pyruvate, insulin, and triglyceride concentrations than obese subjects with poorly controlled type 2 diabetes (Table 1). Fasting glucose, lactate, and pyruvate concentrations of lean and obese diabetic patients were significantly higher than those in lean and obese control subjects, respectively (Table 1). Lactate concentrations between both diabetic groups were not different. No differences in pyruvate levels were detected between obese control subjects and lean patients with type 2 diabetes (Table 1).

Modeling analysis of data from modified FSIGTT

Plasma glucose concentrations of control subjects and diabetic patients during modified FSIGTT are illustrated in Figs. 1 and 2. Obese control subjects were insulin resistant and glucose resistant, compared with lean healthy subjects (S_I, 1.75 ± 0.65 vs. 5.22 ± 1.01 × 10^{-4} $min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$, $P < 0.001$; S_G, 1.79 ± 0.45 vs. 2.68 ± 0.24 × 10^{-2} min^{-1}, $P < 0.01$). S_I of all control subjects was negatively related with fasting glucose ($r = -0.46$, $P < 0.05$), insulin ($r = -0.50$, $P < 0.05$), lactate ($r = -0.65$, $P < 0.001$), and pyruvate concentrations ($r = -0.58$, $P < 0.05$). The AUC for lactate (197.8 ± 19 in lean and 244.3 ± 18 mmol/l × min in obese control, $P = 0.06$) and for pyruvate were increased in obese controls (7,920 ± 624 vs. 6,443 ± 773 μmol/l × min; $P < 0.05$). S_I and S_G of healthy control subjects were not related either to AUC of pyruvate or to AUC of lactate.

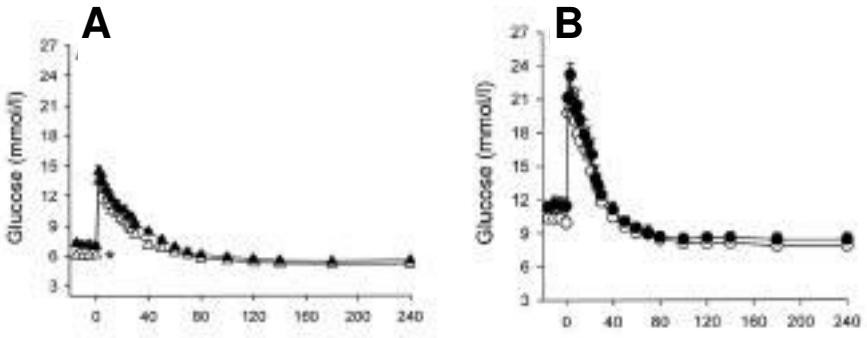

Figure 2—*Mean ± SEM plasma glucose concentrations after FSIGTT of lean patients with type 2 diabetes (A) before (▲) and after (△, *P < 0.05) LA treatment over 4 weeks. Plasma glucose concentrations after FSIGTT of obese patients with type 2 diabetes (B) before (●) and after (○) LA treatment.*

Glucose profiles after FSIGTT of the lean and obese groups with type 2 diabetes are shown in Fig. 2. S_G and S_I were similar in both diabetic groups (Table 2). Comparing AUC of lactate and pyruvate of lean and obese control subjects with those of lean (lactate 272.9 ± 19 mmol/l × min; pyruvate 11,021 ± 669 µmol/l × min) and obese diabetic patients (354.9 ± 34.5 mmol/l × min; pyruvate: 12,242 ± 871 µmol/l × min), respectively, these metabolites are significantly augmented in patients with type 2 diabetes ($P < 0.05$). No relations were found between S_I and S_G with fasting glucose, lactate, and pyruvate as well as the AUC of both glucose metabolites in both diabetic groups. A weak negative relation was detected between S_I and fasting insulin only in the diabetic groups ($r = -0.53$, $P = 0.07$).

Oral administration of LA was associated with increased S_I in lean patients with type 2 diabetes only; however, S_G increased significantly in both groups, but the effect was more prominent in lean than in obese diabetic patients (Table 2). AUC of lactate after intravenous glucose loading decreased in both groups under LA treatment (in lean diabetic patients, 272.9 ± 19 vs. 226.4 ± 18 mmol/l × min after LA, $P = 0.08$; in obese diabetic patients, 354.9 ± 34.5 vs. 255.3 ± 22.4 mmol/l × min; $P < 0.05$). LA treatment was also associated with a decrease of AUC pyruvate from 11,021 ± 669 to 7,921 ± 624 µmol/l × min ($P < 0.01$) in lean patients and from 12,242 ± 871 to 8,723 ± 1,069 µmol/l × min ($P < 0.01$) in obese patients with type 2 diabetes. No correlations were found for S_I and S_G with fasting glucose and insulin, with AUC of pyruvate

Table 2—*Model-derived parameters of S_I and S_G determined by minimal modeling analysis of FSIGTT data from lean and obese type 2 diabetic subjects before and after treatment with LA*

	S_I ($\times 10^{-4}$ min^{-1} · µU^{-1} · ml^{-1}) before	FSD (%)	S_I ($\times 10^{-4}$ min^{-1} · µU^{-1} · ml^{-1}) after	FSD (%)	S_G ($\times 10^{-2}$ min^{-1}) before	FSD (%)	S_G ($\times 10^{-2}$ min^{-1}) after	FSD (%)
Lean type 2 diabetic subjects								
1	2.03	23	2.13	12	1.45	7	1.86	12
2	1.32	16	1.88	11	0.89	3	1.06	10
3	0.79	28	0.56	32	1.68	15	1.96	4
4	1.21	43	1.09	33	1.72	7	1.53	8
5	0.86	9	1.43	15	1.83	23	2.29.	11
6	0.76	3	0.86	23	1.56	14	2.31	6
7	1.88	14	2.42	15	0.89	17	2.14	28
8	1.31	7	1.66	8	0.55	5	1.64	23
9	0.66	4	1.14	9	1.09	8	2.09	12
10	1.99	8	2.38	11	1.10	16	2.38	5
Mean ± SEM	1.28 ± 0.17		1.56 ± 0.21*		1.28 ± 0.14		1.93 ± 0.13*	
Obese type 2 diabetic subjects								
1	0.99	12	1.03	18	1.23	12	1.77	8
2	0.34	25	0.37	28	1.66	14	1.20	6
3	1.35	38	1.45	18	1.35	7	1.72	24
4	1.52	31	1.42	11	0.86	8	1.54	26
5	0.88	12	1.87	9	0.39	21	1.86	17
6	0.23	20	0.67	27	1.09	22	1.52	3
7	1.75	15	1.76	41	1.24	15	1.76	9
8	0.66	9	1.07	22	0.66	4	1.45	17
9	1.50	8	1.29	7	1.21	3	1.29	21
10	0.99	11	1.19	9	0.99	8	1.19	6
Mean ± SEM	1.02 ± 0.16		1.21 ± 0.15		1.07 ± 0.11		1.53 ± 0.08†	

*$P < 0.01$, †$P < 0.05$, before and after treatment with LA in lean and obese type 2 diabetic subjects.

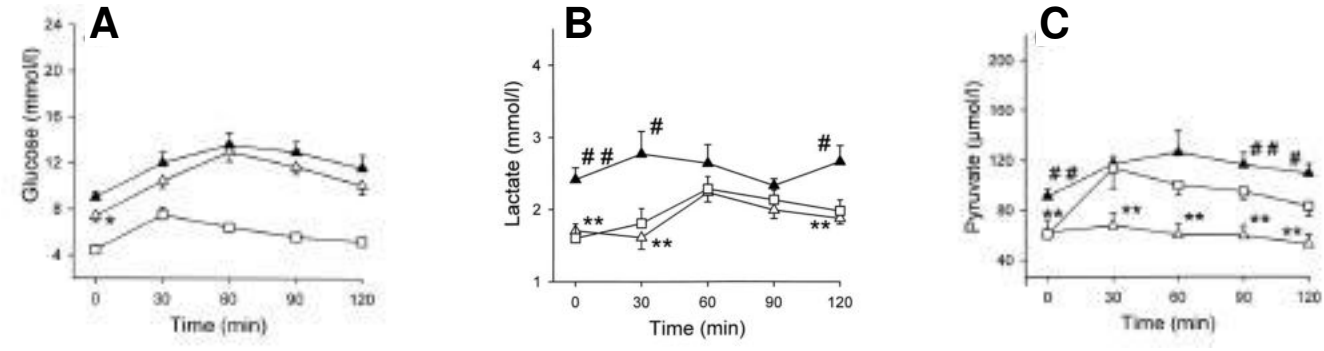

Figure 3—*Mean ± SEM plasma glucose (A), lactate (B), and pyruvate (C) after OGTT from lean control subjects (□), lean patients with type 2 diabetes subjects before (▲); vs. control subjects, ##P < 0.01, #P < 0.05) and after 4-week treatment with LA (△; *P < 0.05, **P < 0.01).*

and lactate in patients with type 2 diabetes after treatment with LA.

OGTT

Higher, but not significant, increments ($P > 0.05$) of glucose concentrations were measured in obese rather than in lean control subjects during OGTT (Figs. 3*A* and 4*A*). MII was twofold higher in obese rather than in lean control subjects (Table 1). OGTT was associated with similar courses of lactate and pyruvate levels in lean and obese control subjects (Figs. 3*B* and *C* and 4*B* and *C*).

Glucose loading caused the highest increments of glucose (from 11.7 ± 0.61 at 0 min to 20.81 ± 1.32 mmol/l at 90 min, $P < 0.001$), lactate (2.76 ± 0.12 at 0 min to 3.82 ± 0.37 mmol/l at 60 min, $P < 0.01$), and pyruvate concentrations (128.87 ± 8.9 at 0 min to 196.4 ± 15.23 µmol/l at 60 min, $P < 0.01$) in obese patients with type 2 diabetes (Figs. 3 and 4). In lean diabetic patients, lactate was higher at 30 and 120 min rather than in lean control subjects (Fig. 3*B*). The initially elevated pyruvate levels did not change during OGTT in lean patients with type 2 diabetes, but were higher than those of lean control subjects at 90 and 120 min (Fig. 3*C*).

Four weeks of treatment with LA resulted in decreased fasting plasma glucose concentrations in lean patients with type 2 diabetes only (Figs. 3*A* and 4*A*). The glucose concentration was reduced 120 min after a oral glucose load ($P = 0.07$) in this group. Fasting lactate dropped significantly in lean and obese patients with type 2 diabetes (Figs. 3*B* and 4*B*). Fasting pyruvate concentrations decreased about >50% in both groups after treatment with LA (Figs. 3*C* and 4*C*).

The application of LA over 4 weeks prevented the increases of lactate and pyruvate concentrations after oral glucose load in both diabetic groups (Figs. 3*B* and *C* and 4*B* and *C*). At this point, lactate levels of lean patients with type 2 diabetes were in the same range as measured in lean control subjects; moreover, pyruvate concentrations were reduced ~46% in lean diabetic patients (Figs. 3*B* and *C*).

In LA-treated obese patients with type 2 diabetes, lactate levels were lower and did not exceed fasting concentrations during OGTT (Fig. 4*B*). Pyruvate levels in LA-treated obese patients, however, were twofold decreased and were lower than those in obese control subjects after glucose load.

No change in mean incremental insulin was observed in obese diabetic subjects and in lean patients with type 2 diabetes; however, mean incremental insulin was significantly decreased from 230.41 ± 11.5 to 193.5 ± 13.18 pmol/l ($P < 0.05$) after 4 weeks of LA treatment. Hydroxybutyrate concentrations were not increased and did not change significantly in both groups before and after treatment (data not shown). BMI and triglycerides were not different after LA treatment (data not shown). HbA_{1c} was slightly decreased in lean patients with type 2 diabetes only (6.5 ± 0.2 vs. 6.1 ± 0.2%, $P = 0.08$)

CONCLUSIONS — Four weeks of treatment with lipoic acid reduced fasting lactate and pyruvate concentrations in both diabetic groups and prevented the increments of pyruvate and lactate after glucose loading. In lean diabetic patients, LA treat-

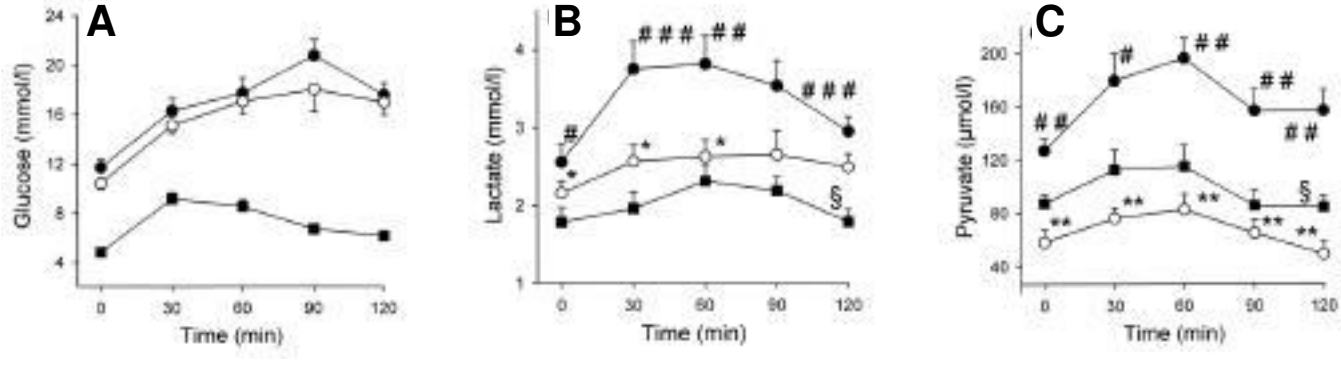

Figure 4—*Mean ± SEM plasma glucose (A), lactate (B), and pyruvate (C) after OGTT from obese control subjects (■), obese patients with type 2 diabetes subjects before (●) vs. control subjects (#P < 0.05, ##P < 0.01, ###P < 0.001) and after 4-week treatment with LA (○), *P < 0.05, **P < 0.01; vs. control subjects (§P < 0.05).*

ment was associated with significantly reduced fasting glucose concentrations (Figs. 2 and 3*A*) and improved S_I and S_G (Table 2). The improved S_I was reflected by a significant reduction of mean incremental insulin during OGTT in these patients. S_G increased in obese patients with type 2 diabetes also, and insulin sensitivity rose but the differences were not significant (Table 2). Taniguchi et al. (20) investigated patients with type 2 diabetes with good glycemic control (HbA_{1c} 6.55 ± 0.48) with similar S_G as determined in our lean and obese diabetics with good and poor glycemic control, respectively. Therefore, we suggest that differences in glycemic control do not influence S_G in type 2 diabetes. In addition, Finegood et al. (26) could detect similar results in patients with type 1 diabetes. Insulin sensitivity before treatment was similar in lean and obese patients before treatment, confirming that type 2 diabetes per se is the major contributor to insulin resistance and not obesity (27).

An inverse relationship between S_I and basal lactate was found in lean and obese control subjects, indicating that insulin resistance is associated with increasing fasting lactate levels (28). Although close relationships between S_I and AUC lactate as well as S_G and lactate (28,29) have been reported, we found no correlations between these parameters. Different study subjects and experimental settings may explain these differences. The lack of such relations between S_I and S_G with these metabolic parameters in patients with type 2 diabetes may reflect the multiple pathways leading to glucose and insulin resistance in patients with type 2 diabetes.

Fasting lactate concentrations were elevated in diabetic patients only. Fasting pyruvate levels, however, were significantly higher in insulin-resistant obese subjects than in lean control subjects and were also higher in in obese diabetic patients with poor glycemic control than in lean diabetic patients (Table 1, Figs. 3*B* and *C* and 4*B* and *C*). High lactate and pyruvate levels in our obese control subjects may support the finding that glucose oxidation is already impaired in normoglycemic, obese control subjects with hyperlipidemia, probably caused by the release of higher free fatty acids which impair PDH activity (30).

Impairment of glucose transport, glucose phosphorylation (31), and nonoxidative and oxidative glucose disposal in muscle tissue (32) contribute to the insulin resistance in patients with type 2 diabetes. Glucose-stimulated glucose uptake is the major contributor to glucose disposal after FSIGTT (33). The mechanism by which glucose facilitates its own uptake is currently not known. However, studies in animals and humans (34,35) suggest that the acute rise of glucose is able to induce an acute translocation of glucose transporters to the plasma membrane in muscle tissue, thus enhancing glucose uptake independent of insulin action. Therefore, impaired transmembrane glucose transport (36), a defect in nonoxidative and oxidative pathways (14,21) in diabetic subjects, is thought to be involved in the decreased ability of glucose to enhance its own uptake in patients with type 2 diabetes. Experimental data suggest that LA may act on several steps by increasing insulin-stimulated glucose transport activity, nonoxidative glucose disposal and glucose oxidation in peripheral tissue, such as skeletal muscle (2–4,6). Since fasting hyperglycemia in patients with type 2 diabetes is primarily caused by impaired hepatic gluconeogenesis (37), we can also suggest that LA may ameliorate metabolic processes in hepatic tissue. Experimental data support this assumption demonstrating that LA application decreased hepatic ketone body production (6) and gluconeogenesis (38).

Because pyruvate concentrations were reduced after LA treatment, we also suggest that LA may stimulate aerobic glucose oxidation at the level of mitochondrial PDH, as experimentally shown (6). This suggestion would imply that more pyruvate would enter the Krebs cycle and would contribute to an enhanced generation of intracellular energy-rich phosphates. Experimental studies also showed (39,40) that LA enhanced glucose uptake and glucose utilization in diabetic rat hearts. These effects were associated with the elevation of energy production and higher cardiac output. It remains controversial, however, whether the effects on lactate and pyruvate metabolism of LA are due only to an interaction with the PDH complex. However, such an effect would tend to shunt more lactate into carbon dioxide formation and to provide less substrate for hepatic gluconeogenesis. Therefore, it would explain the lower fasting glucose, lactate, and pyruvate concentrations after LA administration in our study. Earlier experimental data showed that LA, as well as the PDH-stimulating substance, dichloroacetate, lowered pyruvate and blood glucose in diabetic rats. Furthermore, LA reduced acetoacetate levels, whereas dichloroacetate administration had no effect (6). Singh and Bowman (41) noted markedly increased phosphofructokinase activity and subsequent higher glycolysis in rat muscle after LA admistration. Thus, stimulation of PDH alone cannot explain all the metabolic effects of LA.

However, we must mention that lactate and pyruvate concentrations were measured in venous blood of the forearm, and therefore, the exact origin of these metabolites cannot be identified. Venous blood pyruvate levels to some extent reflect changes in metabolism of local tissues and are not necessarily indicative of events in the body as a whole. Considering the findings of Avogaro et al. (16), that an increased intracellular pyruvate-lactate interconversion exists in the forearm muscle of patients with type 2 diabetes, the elevated levels of these metabolites in venous blood may derive from this tissue. The authors suggested that the most probable cause for the diminished pyruvate degradation in patients with type 2 diabetes may lie in a defect of glucose oxidation located at the level of PDH since the rate of pyruvate oxidation is primarily determined by the activation of PDH (16,42). A decrease in PDH activity would result in a reduced oxidation of pyruvate to acetyl-CoA and would contribute to an increased conversion of pyruvate to lactate via lactate dehydrogenase (11) with a subsequent increment of lactate.

Our study shows that reduced activity of PDH becomes more apparent after an acute rise of glucose during oral and intravenous glucose tests (Figs. 3*B* and *C* and 4*B* and *C*) in diabetic patients. Lactate concentrations after OGTT are the result of increased storage of this metabolite of glucose oxidation in the basal state that then, after glucose loading, leave the tissue (43). Therefore, lactate reached the highest concentrations in the obese patients with type 2 diabetes (Fig. 2*B*) since glucose recycling rate (44) and lactate production by adipose tissue are markedly elevated in obese patients with type 2 diabetes (11,28,45). While the increased lipid oxidation in obese patients with type 2 diabetes explains the decreased glucose oxidation (30), this mechanism fails to explain the defects in glucose oxidation in lean patients with type 2 diabetes (46). Our results support the findings described above that there is a defect in glucose oxidation that cannot be overcome by increasing insulin concentrations and cannot be explained by obesity, impaired fat oxidation, and reduced glucose uptake (15).

In humans there are no descriptions of LA deficiency; however, lower concentrations have been found in patients with acne vulgaris, neurodermatitis, liver cirrhosis, advanced arteriosclerosis, psoriasis, different types of polyneuropathy, and diabetes (47). Therefore, the question arises whether LA deficiency can be one of the reasons for the impaired glucose metabolism in patients with type 2 diabetes. Serum α-lipoic acid concentrations in humans are very low and thus very difficult to measure (Pharma Research, ASTA); therefore, LA deficiency is difficult to assess. However, it seems to be conceivable that the increased oxidative stress in patients with type 2 diabetes (48) consumes the antioxidative capacity of free radical scavangers, such as LA (49). Thus, the supplementation of this vitamin-like substance in diabetic subjects may improve both antioxidant defenses and glucose metabolism.

This study yields some evidence that impaired glucose oxidation after glucose loading in patients with type 2 diabetes is associated with augmented lactate and pyruvate production. No placebo-controlled group was used in this study. Thus, a study effect cannot be ruled out and weakens the study results. Nevertheless, the marked differences and the consistency of the results make a study effect unlikely. Therefore, oral treatment with LA seems to improve intracellular glucose utilization, probably by stimulating PDH, and increases glucose-mediated glucose disposal in patients with type 2 diabetes.

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