Short-Term Hyperglycemic Dysregulation in Patients With Type 1 Diabetes Does Not Change Myocardial Triglyceride Content or Myocardial Function

Sebastiaan Hammer, msc[1,2]
Jacqueline T. Jonker, md[1,2]
Hildo J. Lamb, md, phd[2]
Rutger W. van der Meer, md[2]
Wendy Zondag, md[1]
Jan M. Sepers, md, phd[3]
Albert de Roos, md, phd[2]
Johannes W.A. Smit, md, phd[1]
Johannes A. Romijn, md, phd[1]

OBJECTIVE — To evaluate the effects of hyperglycemia due to partial insulin deprivation on myocardial triglyceride (TG) content and myocardial function in patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS — Myocardial and hepatic TG content and left ventricular (LV) function were measured by magnetic resonance (MR) spectroscopy and MR imaging during optimal glucoregulation and after 24 h of partial insulin deprivation ($n = 10$).

RESULTS — Mean insulin infusion rate was 45 ± 5 units at baseline, whereas it was 27 ± 5 units during hyperglycemia (per 24 h, $P < 0.001$). Plasma glucose levels increased from 8.4 ± 0.6 to 15.9 ± 0.8 mmol/l ($P < 0.001$), and plasma levels of nonesterified fatty acids from 0.31 ± 0.05 to 0.46 ± 0.07 mmol/l ($P = 0.015$). Hyperglycemia had no effects on myocardial or hepatic TG content and LV function.

CONCLUSIONS — Short-term hyperglycemic dysregulation does not modulate myocardial or hepatic TG content or myocardial function, despite considerable metabolic adaptations.

Diabetes Care **31:1613–1614, 2008**

Intramyocellular triglyceride (TG) content in skeletal muscle is increased in patients with type 1 diabetes compared with that in control subjects (1), suggesting a major role of metabolic dysregulation in the induction of abnormal intramyocellular lipid accumulation in type 1 diabetes. Recent optimalization of magnetic resonance (MR) spectroscopy techniques allowed us to study myocardial TG content and myocardial function in vivo and to document an inverse relationship between myocardial TG content and myocardial function in healthy subjects (2). Therefore, we hypothesized that episodes of metabolic dysregulation due to insufficient insulin provision may adversely affect myocardial TG content and myocardial function.

RESEARCH DESIGN AND METHODS

— MR imaging and MR spectroscopy were performed twice in 10 C-peptide–negative, nonsmoking patients with type 1 diabetes (five male) using insulin treatment by insulin pump therapy (continuous subcutaneous insulin infusion). No participant showed evidence of cardiovascular disease. The study was designed to mimic hyperglycemic dysregulation in daily life. Therefore, the subjects were instructed to retain their daily routine. One study was done after a 3-day period in which subjects aimed at optimal blood glucose levels measured by a continuous glucose monitoring system (Medtronic). The second study was performed after ~50% reduction in basal and bolus insulin infusions during 24 h, compared with the first study, in order to maintain hyperglycemia with glucose levels between 15 and 20 mmol/l. For both occasions, patients were instructed to maintain the same caloric intake for 3 days before examination. The sequence between the euglycemic and hyperglycemic occasions was randomly assigned. Before MR examination, blood samples (postprandial) were taken. An ethics committee approved the study, and subjects signed informed consent.

MR spectroscopy measurements (1.5-T; Philips) were obtained using a point-resolved, spatially localized spectroscopic pulse sequence to acquire single voxel (8 ml) spectra. For the heart, data acquisition was double triggered (electrocardiogram triggering and navigator echoes [3]). For the liver, voxel sites were matched at the study occasions. Lipid resonances of myocardial and hepatic TG were summed and calculated as a percentage of the unsuppressed water signal ([TG/water] × 100).

To assess left ventricular (LV) systolic function, the heart was imaged in the short axis orientation. To assess LV diastolic function, a phase contrast sequence with velocity encoding was performed to measure blood flow across the mitral valve (4). Analysis was performed using MASS and FLOW (Medis) to quantify LV ejection fraction and flow velocities in early diastole (early filling phase [E]) and at atrial contraction (atrial filling phase [A], E/A ratio, and E deceleration).

Data were compared by paired *t* test and are shown as mean ± SEM. $P < 0.05$ was considered to reflect significant differences.

RESULTS

— Patient characteristics at baseline and during hyperglycemia are shown in Table 1. During partial insulin deprivation, hyperglycemic dysregula-

From the [1]Department of Endocrinology, Leiden University Medical Center, Leiden, the Netherlands; the [2]Department of Radiology, Leiden University Medical Center, Leiden, the Netherlands; and the [3]Department of Internal Medicine, Medical Centre Alkmaar, Alkmaar, the Netherlands.
Corresponding author: S. Hammer, s.hammer@lumc.nl.
Received 12 March 2008 and accepted 30 April 2008.
Published ahead of print at http://care.diabetesjournals.org on 5 May 2008. DOI: 10.2337/dc08-0513.

Table 1—*Clincial, MR spectroscopy, and MR imaging parameters at baseline and during partial insulin deprivation*

	Baseline	Partial insulin deprivation	*P*
Clinical characteristics			
Age (years)	41 ± 3	—	—
A1C (%)	7.4 ± 0.2	—	—
Duration of diabetes (years)	21.7 ± 2.3	—	—
BMI (kg/m^2)	23.5 ± 0.6	23.0 ± 0.8	0.1
Mean 24-h glucose (mmol/l)	8.4 ± 0.6	15.9 ± 0.8	< 0.001
Mean 24-h insulin (units/l)	45 ± 5	27 ± 5	< 0.001
NEFAs (mmol/l)	0.31 ± 0.05	0.46 ± 0.07	0.015
TG (mmol/l)	1.03 ± 0.24	0.85 ± 0.49	0.2
Total cholesterol (mmol/l)	4.3 ± 0.2	4.4 ± 0.2	0.1
Systolic blood pressure (mmHg)	114 ± 4	118 ± 5	0.2
Diastolic blood pressure (mmHg)	68 ± 3	73 ± 3	0.1
Heart rate (bpm)	63 ± 1	60 ± 3	0.3
MR spectroscopy			
Liver TG content (%)	0.77 ± 0.09	0.84 ± 0.11	0.4
Myocardial TG content (%)	0.31 ± 0.04	0.34 ± 0.06	0.6
MR imaging			
LV ejection fraction (%)	58 ± 1	59 ± 2	0.6
E peak filling rate (ml/s)	475 ± 21	467 ± 20	0.6
E deceleration (ml/s^2 × 10^{-3})	4.4 ± 0.4	4.5 ± 0.3	0.8
A peak filling rate (ml/s)	267 ± 21	254 ± 38	0.7
E/A peak ratio	1.9 ± 0.2	1.9 ± 0.3	0.9

Data are means ± SEM. Blood samples were obtained 2 h after the last meal. NEFA, nonesterified fatty acid.

tion was present in all patients (mean plasma 24-h glucose was 8.4 ± 0.6 mmol/l during the control study, which increased to 15.9 ± 0.8 mmol/l during partial insulin deprivation [$P < 0.001$]) and associated with an increase in plasma levels of nonesterified fatty acids from 0.31 ± 0.05 to 0.46 ± 0.07 mmol/l ($P = 0.015$). Myocardial TG content was 0.31 ± 0.04% at baseline and did not change during hyperglycemic dysregulation (0.34 ± 0.06%; $P = 0.587$). E/A ratio was unaffected (1.9 ± 0.2 at baseline vs. 1.9 ± 0.3).

CONCLUSIONS — This is the first study to document the effects of short-term hyperglycemic dysregulation on myocardial TG content and LV function in patients with type 1 diabetes. The present study shows that hyperglycemic dysregulation for 24 h, as frequently observed in patients with type 1 diabetes, does not modulate myocardial TG content or myocardial function, despite considerable metabolic dysregulation.

We hypothesized that short-term partial insulin deprivation results in changes in myocardial TG content, possibly associated with changes in myocardial function. Stiffness of intermediate-sized arteries is rapidly increased in patients with type 1 diabetes during hyperglycemia, whereas larger arteries seem unaffected (5). Moreover, in healthy subjects myocardial function and TG content rapidly adapt to changes in metabolic state (2). Interestingly, this adaptation could not be evoked by short-term hyperglycemic dysregulation, suggesting that the heart is protected from these short-term effects. Nonetheless, we cannot exclude the possibility that prolongation of the duration of partial insulin deprivation might have resulted in changes in myocardial function and TG content.

Patients with type 1 diabetes have considerably altered myocardial glucose and fatty acid metabolism. Myocardial fatty acid utilization is increased, whereas myocardial glucose uptake is considerably lower in diabetic patients compared with that in control subjects (6). These adaptations protect the heart-to-substrate overflow of the myocardium. Accordingly, the present study interestingly shows that myocardial TG content in diabetic patients was not different from the values we observed in studies in healthy subjects (2,3). However, fatty acid kinetics during hyperglycemia cannot be derived from the present data, and we cannot exclude changes in myocardial fatty acid oxidation.

Hepatic TG content was measured to study the effects of insulin deprivation on tissue-specific TG distribution because we previously found discrepant effects of interventions on heart and liver (2). However, in the present study design insulin deprivation did not result in altered hepatic TG content.

In conclusion, short-term partial insulin deprivation resulting in hyperglycemic dysregulation, which is frequently observed in patients with type 1 diabetes, does not modulate myocardial or hepatic TG content or LV function, despite considerable metabolic dysregulation.

Acknowledgments— We thank Marja Dijk-Schaap and Nathalie Masurel for their assistance with the study.

References

1. Perseghin G, Lattuada G, Danna M, Sereni LP, Maffi P, De CF, Battezzati A, Secchi A, Del MA, Luzi L: Insulin resistance, intramyocellular lipid content, and plasma adiponectin in patients with type 1 diabetes. *Am J Physiol Endocrinol Metab* 285: E1174–E1181, 2003
2. Hammer S, van der Meer RW, Lamb HJ, Schar M, de Roos A, Smit JW, Romijn JA: Progressive caloric restriction induces dose-dependent changes in myocardial triglyceride content and diastolic function in healthy men. *J Clin Endocrinol Metab* 93:497–503, 2008
3. van der Meer RW, Doornbos J, Kozerke S, Schar M, Bax JJ, Hammer S, Smit JW, Romijn JA, Diamant M, Rijzewijk LJ, de Roos A, Lamb HJ: Metabolic imaging of myocardial triglyceride content: reproducibility of 1H MR spectroscopy with respiratory navigator gating in volunteers. *Radiology* 245:251–257, 2007
4. Hartiala JJ, Mostbeck GH, Foster E, Fujita N, Dulce MC, Chazouilleres AF, Higgins CB: Velocity-encoded cine MRI in the evaluation of left ventricular diastolic function: measurement of mitral valve and pulmonary vein flow velocities and flow volume across the mitral valve. *Am Heart J* 125:1054–1066, 1993
5. Gordin D, Ronnback M, Forsblom C, Heikkila O, Saraheimo M, Groop PH: Acute hyperglycaemia rapidly increases arterial stiffness in young patients with type 1 diabetes. *Diabetologia* 50:1808–1814, 2007
6. Peterson LR, Herrero P, McGill J, Schechtman KB, Kisrieva-Ware Z, Lesniak D, Gropler RJ: Fatty acids and insulin modulate myocardial substrate metabolism in humans with type 1 diabetes. *Diabetes* 57: 32–40, 2008