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

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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 TG content and left ventricular (LV) function were measured by magnetic resonance (MR) spectroscopy and MR imaging during optimal glucoregulation and after 24 hours 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 hours, 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 non-esterified fatty acids from 0.31 ± 0.05 to 0.46 ± 0.07 mmol/l (P = 0.015). Hyperglycemia had no effects on myocardial TG content and LV function.

Conclusions: Short-term hyperglycemic dysregulation does not modulate myocardial TG content or myocardial function, despite considerable metabolic adaptations.
Intramyocellular triglyceride (TG) content in skeletal muscle is increased in patients with type 1 diabetes compared to controls (1), suggesting a major role of metabolic dysregulation in the induction of abnormal intramyocellular lipid accumulation in type 1 diabetes. Recent optimization of magnetic resonance (MR) spectroscopy techniques allows to study myocardial TG content and myocardial function in vivo, and documented an inverse relation 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 was performed twice in 10 C-peptide negative, non-smoking patients with type 1 diabetes (5 men), 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 hours, 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 prior to examination. The sequence between the euglycemic and hyperglycemic occasions was randomly assigned. Prior to MR examination blood samples (post-prandial) were taken. Ethical approval was obtained 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 (ECG 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, an 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 (E) and at atrial contraction (A, E/A ratio and E deceleration).

Data was 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 dysregulation was present in all patients (mean plasma 24-hour-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 \( (P < 0.001) \), associated with an increase in plasma levels of non-esterified fatty acids (NEFAs) 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 %,
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 hours, 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 can not 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 patients compared to controls (6). These adaptations protect the heart to substrate overflow of the myocardium. Accordingly, the present study interestingly shows that myocardial TG content was not different in patients from the values we observed in studies in healthy subjects (2,3). However, fatty acid kinetics during hyperglycemia can not be derived from the present data and we can not 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 TG content or LV function, despite considerable metabolic dysregulation.

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| Clinical characteristics        | Baseline | Partial insulin deprivation | $P$ value |
|--------------------------------|----------|----------------------------|-----------|
| Age (years)                    | 41 ± 3   |                            |           |
| HbA1c (%)                      | 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 24h glucose (mmol/l)      | 8.4 ± 0.6| 15.9 ± 0.8                 | < 0.001   |
| Mean 24h insulin (U/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$^2$ x 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       |

Blood samples were obtained 2 hours after the last meal. HbA1c = glycated hemoglobin, NEFAs = non-esterified fatty acids, TG = triglyceride, MR = magnetic resonance, LV = left ventricular, E = early filling phase, A = atrial filling phase. Data are compared to baseline and shown as mean ± SEM.