Fuel Metabolism During Exercise in Eu- and Hyperglycemia in Subjects with Type 1 Diabetes Mellitus

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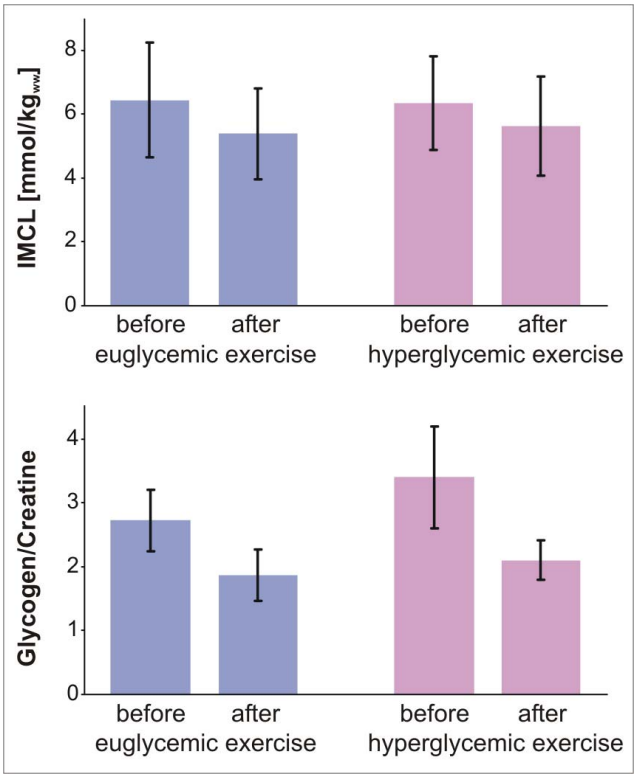
Introduction: Many patients with type 1 diabetes mellitus (T1DM) are regularly involved in physical exercise; some even participating in competitive sports. Despite this fact, little is known about the effect of blood glucose levels on local muscle fuel metabolism during exercise in individuals with T1DM. Preliminary data revealed similar exercise capacities in eu- compared to hyperglycemic conditions. Therefore it was the goal of this study to investigate the effect of prolonged aerobic exercise under either eu- or hyperglycemic clamp conditions on the muscle's major energy stores, intramyocellular lipids (IMCL), and muscular glycogen.

Methods: Seven young male individuals (age = 33.5 ± 6.3 years (mean ± standard deviation); BMI = 24.1±1.2 kg/m^2) with T1DM (diabetes duration was 20.1±9.4 years and HbA_{1c} reflected good glycemic control (6.7 ± 0.5%)) under continuous subcutaneous insulin infusion (CSII) were studied on two occasions. After discontinuation of CSII on the evening before each trial, a variable i.v. insulin infusion was started to reach normal glucose levels overnight. The volunteers were kept fasting. At 8 am of the next day blood glucose was clamped to euglycemic (target level 5 mmol/l) or hyperglycemic levels (target level 11 mmol/l) in a randomized, single blinded, cross-over design. Insulin infusion was kept constant according to the patient's CSII basal insulin rate. When stable clamp conditions were reached, IMCL and muscular glycogen (M. quadriceps) were measured using 1H- and 31C-MR spectroscopy. Immediately after this MRS session the volunteers cycled for two hours at a constant power corresponding to 55-60% of their VO_{2max} (previously determined in a separate session). Respiratory exchange ratio (RER) was measured by spirometry. Immediately after the exercise IMCL and muscular glycogen were measured again. Results of the two tests were compared using Student's paired t-test.



MRS experiments were performed on a SIGNA 1.5 Tesla whole-body MR-system (General Electric) using a flexible 13C/1H double-tuned coil (Medical Advance, Milwaukee WI) located over the *m.quadriceps femoris*. Single voxel ^{1}H-MR spectra were acquired with a short echo time PRESS sequence (TE 20 ms, 12 x 11 x 18 mm3 in m.vastus intermedius). IMCL were quantified in absolute units (mmol per kg wet weight; mmol/kg$_{ww}$) as described earlier [1]. ^{13}C-MR spectra were acquired with a pulse-and-acquire sequence (adiabatic excitation, TR 165 ms, 3 x 4000 acquisitions) applying CW decoupling and NOE buildup (home-built second channel). Glycogen results are shown as ratios relative to the Creatine signal. Mean variance of the Creatine signal was 5.9 ± 2.4 % for all volunteers.

Results: Euglycemic clamps were at a mean blood glucose level of 5.0 mmol/l, whereas the mean glucose level was at 10.9 mmol/l in hyperglycemic clamps (difference 5.9 mmol/l, $p < 0.0001$). Mean insulin levels were 17mU/l and did not differ between eu- and hyperglycemic clamp conditions. To maintain hyperglycemia 9.5 mg/min mean glucose infusion rates were needed (4.4 mg/min to maintain euglycemia; p = 0.001). The results of the MR measurements are shown in the figure. Depletion of IMCL during exercise tended to be more ($p = 0.18$) pronounced during eu- (16.2%, p = 0.003) compared to hyperglycemic (11.5%, p = 0.088) exercise condition. In contrast, glycogen consumption was significant (p << 0.05) during both clamp conditions with a similar reduction (31.2% vs. 38.1%, p=0.56). RER was significantly lower in eu- compared to hyperglycemic conditions (0.84 and 0.93, $p = 0.034$), reflecting a higher net lipid oxidation rate in euglycemic exercise condition.

Discussion & Conclusions: For individuals with T1DM performing aerobic exercise lipid oxidation appears to play a predominant role in euglycemia when IMCL and free fatty acids are suggested to be the main fuel source. In contrast, during hyperglycemia energy production appears to rely stronger on carbohydrate oxidation. Of note, the latter did not result in an increased consumption of muscular glycogen thereby suggesting that the increased levels of blood glucose provided the main energy substrate in hyperglycemia.

References: [1] Boesch C et al. *NMR in Biomedicine* 2006 **19**: 968–988.

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