Correlation of insulin sensitivity and replenishment of intramyocellular lipids (IMCL) as observed by ^{1}H-MRS

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Introduction: Intramyocellular lipid (IMCL) levels as observed by ^{1}H-MR spectroscopy correlate with insulin sensitivity ([1] and refs therein). However, this correlation shows a complex U-shaped behavior since both insulin resistant diabetes patients and highly insulin sensitive athletes show high levels of IMCL while sedentary subjects with intermediate insulin sensitivity have low IMCL stores [2]. We hypothesize that variation of IMCL levels (depletion and replenishment) are unambiguously correlated with insulin sensitivity and training status. Since an earlier report did not find such dependence in *m.tibialis anterior* [3], both *quadriceps* and *tibialis anterior* muscles were measured in nine subjects with a large range of insulin sensitivity and training status.

Methods: Nine volunteers (3 diabetes patients, 3 sedentary healthy subjects, and 3 athletes) were enrolled in this pilot study, which was approved by the institutional ethical committee. Muscular insulin sensitivity was assessed by monitoring whole-body glucose infusion rates (GIR) during a two-step hyperinsulinemic euglycemic clamp (diabetes patients ceased the intake of oral anti-diabetic medication for 24 hours). The training status was estimated by VO_{2peak} determined on a treadmill following a modified Bruce protocol. Distributions of insulin sensitivity (GIR) and training status (VO_{2peak}) of the volunteers are shown in Fig.1. In order to reduce IMCL levels in all three groups with obviously very large differences in physical capacity, a moderate combination of low fat diet (individual diet based on instructions and controlled by diary) and daily physical activity (1 hour/day walking/jogging, heart rate controlled at approximately 70% VO_{2peak}) over three days has been applied. For replenishment of IMCL levels, a fat rich diet (3 additional snacks between regular meals) and minimal physical activity were performed the following 48 hours with MRS examinations at 0, 11, 24 and 48 hours. IMCL were determined by means of ^{1}H-MRS (single voxel PRESS sequence, TR=3s, TE=20ms, 128 acquisitions, 16 phase rotation steps, water and outer volume suppression) in a 1.5 Tesla MR system (GE SIGNA) using an rigid extremity (calf) and a flexible Helmholtz coil (thigh). The voxels ($11\times12\times18mm^3$) were placed in the *vastus intermedius* and the *tibialis anterior* muscle. Following eddy current correction, spectra were fitted with TDFDFIT [4] and quantified using the fully relaxed water signal as internal standard [1].

Results: The volunteers show a highly significant correlation between training status and insulin sensitivity (Fig.1, $p = 0.002$, $r = 0.875$). The GIR and the VO_{2peak} of the diabetes patients is close to that of the sedentary subjects representing the fact that two of the diabetes patients enrolled in this pilot study are physically active. Fig.2 shows the significant correlation of the IMCL replenishment in the first 11 hours in the *vastus* muscle ($p = 0.014$, $r = 0.779$) with the glucose infusion rate. The correlation of the IMCL replenishment in 11 hours with VO_{2peak} ($p = 0.038$, $r = 0.693$) and BMI ($p = 0.009$, $r = 0.803$) are also significant in the *vastus* muscle. Correlations between IMCL replenishment in the later MRS-examinations (24 hours and 48 hours) do not reach significance. In addition, correlations between IMCL replenishment and GIR or VO_{2peak} are uncorrelated in *m.tibialis anterior*.

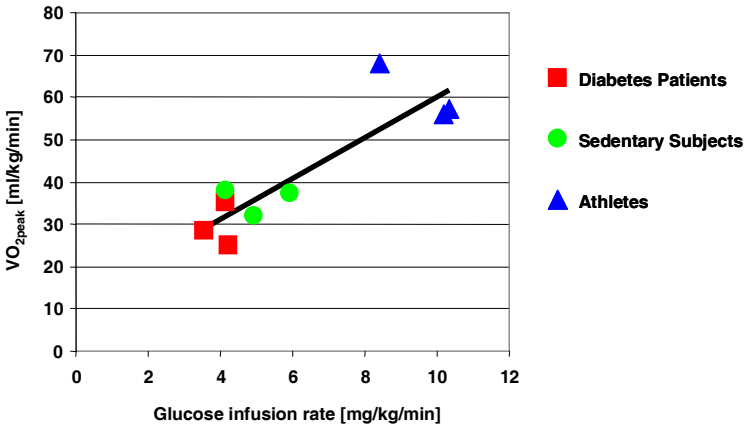

Fig.1: Correlation of training status and insulin sensitivity

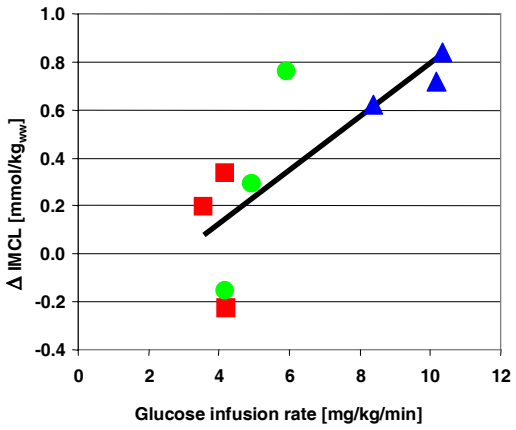

Fig.2 Correlation of IMCL replenishment and insulin sensitivity

Discussion: The findings in the *vastus muscle* are significant for the initial 11 hours of replenishment. The fact that the replenishment during the following hours is no longer correlated with insulin sensitivity may have several reasons including a less stringent control of physical activity over 48 as compared to 11 hours and non-linear effects such as a possible overshoot of IMCL during replenishment. An earlier report did find differences of replenishment in the *m.tibialis anterior* depending on the type of diet, however, not on the training status [3]. The present study is in agreement with this report since it finds a correlation for the *vastus* muscle only, not for the *m.tibialis anterior*. Depletion of IMCL levels in athletes and healthy subjects is well established, however, it represents a crucial problem if subjects with enormous differences of their physical activity should be compared. Our experience with patients and athletes has shown in the past that a rather moderate daily activity combined with a low fat diet can reduce IMCL to levels that cannot be further reduced without exhausting activities that are impossible for patients. Therefore, we conclude that IMCL levels at the time of the first MR exam have been as low as reasonably achievable. In addition, since an increase instead of a single concentration is measured, the measurement may be robust against small variations of the starting level, at least for the first 11 hours of replenishment.

Conclusions: Even if the limitations of this pilot study (number of volunteers, moderate control of depletion and replenishment) are considered, the results show an unequivocal correlation between the ability of the vastus muscle to store/use IMCL and its insulin sensitivity and training status, respectively. This finding extends our understanding of the relation between insulin action and IMCL metabolism.

References: [1] Boesch C et al. NMR Biomed 2006;**19**:968-988 [2] Thamer C et al. J Clin Endocrinol Metab 2003;**88**:1785-1791 [3] Decombaz J et al. Am J Physiol 2001;**281**:R760-R769 [4] Slotboom J et al. Magn Reson Med 1998;**39**:899-911

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