Abnormal Exercise Function in Adolescents with Type 2 Diabetes Correlates Negatively with Soleus Muscle IMCL As Measured by 1H MRS

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Introduction:

Adults with type 2 diabetes (T2D) exhibit impaired maximal exercise capacity (VO_2max) even in the absence of diabetic complications. In this study, we investigated whether this exercise dysfunction is already present in youth. We hypothesized that VO_2max is already reduced in adolescents with T2D, and is associated with impaired insulin sensitivity, endothelial dysfunction, and inflammation. The hypothesis was tested by measurements of muscle extramyocellular lipids (EMCL) and intracellular lipids (IMCL) using ^{1}H magnetic resonance spectroscopy (^{1}H MRS), VO_2max, blood flow, autonomic function, body composition, inflammatory markers, and insulin sensitivity in lean, obese, and T2D adolescents.

Methods:

Thirty-seven adolescents (13 T2D, 13 obese, and 11 lean) had similar age, sex, Tanner stage, and activity level. Body Mass Index (BMI) was similar in the obese and T2D groups. Following three days of a standardized study diet, all subjects underwent measurement of VO_2max, blood flow (venous plethysmography), autonomic function, body composition (DEXA), inflammatory markers, insulin sensitivity (hyperinsulinemic euglycemic clamp), and muscle lipids in the soleus and tibialus anterior muscles (^{1}H MRS).

The MRS measurements were performed on a GE 3T whole body (long bore) scanner, using a standard extremity coil. Non-solvent suppressed spectra (TR/TE=2000ms/100ms, 128 avg., nominal voxel size 5 cm^3) were acquired using the PROBE-P (PRESS) sequence. The entire MR exam, including appropriate localizer images and the spectral aquisitions on the two different muscles took less than 25 min. Care was taken in placing the spectroscopy voxels to avoid visible fat and fasciae lines between muscle groups. Spectra degraded by motion were repeated. The results were analyzed using LCModel software[1], with an appropriate muscle basis set which analyzes for EMCL, IMCL, creatine, choline, and taurine.

Results:

Significantly increased IMCL levels of both soleus and tibialis anterior were found between the T2D group versus the other two groups. Significant differences in soleus EMCL were found between the lean group vs. the obese group, the lean group vs. the T2D group, and the obese vs. T2D groups. No significant differences were found between any of the groups in the tibialis EMCL levels. These results are summarized in Table 1.

VO_2max/kg was significantly lower in T2D vs. obese vs. lean subjects (21.9 ± 4.2 vs. 28.7 ± 5.2 vs. 41.2 ± 10.2 ml/kg/min, all $p<0.005$). VO_2max/kg significantly correlated positively with insulin sensitivity (mg/kg/min) ($r=0.82$, $p<0.0001$), and negatively with blood flow ($r= -0.59$, $p<0.0001$), hemoglobin a-1c ($r= - 0.55$, $p <0.0001$), C-reactive protein ($r= -0.50$, $p=0.003$) and myeloperoxidase ($r= -0.40$, $p=0.027$). In addition, soleus IMCL also correlated negatively with VO_2max/kg ($r= -0.645$, $p<0.0001$).

Table 1: Muscle Fat Distribution

	Lean	Obese	T2D
Soleus EMCL	1271 ± 661	3331 ± 2299*	3005 ± 863**
Tibialis EMCL	747 ± 709	1921 ± 1654	1909 ± 807
Soleus IMCL	1166 ± 458	2014 ± 947	2935 ± 1006**^
Tibialis IMCL	351 ± 105	372 ± 269	687 ± 260***^^

*p=0.017 vs. lean, **p<0.0001 vs. lean, ***p=0.009 vs. lean, ^p=0.036 vs. obese, ^^p=0.022 vs. lean

Discussion

VO_2max inversely correlates with IMCL, as well as with markers of insulin sensitivity, endothelial function, and inflammation. Of concern, VO_2max is significantly reduced even in adolescents with T2D, not explainable by body weight or inactivity. Thus, muscle fuel metabolism appears to be abnormal in youth with T2DM, and may contribute to their exercise dysfunction. This observation is consistent with previous results showing increased IMCL in adolescent type 1 diabetics (T1D)[2]. We are now expanding our study to include T1D adolescents. VO_2max also was inversely associated with glycemia, in contrast to studies in adults. We conclude that a reduction in VO_2max is a defect found early on in subjects with T2D and therefore is intrinsically linked to the pathophysiology of T2D.

References:

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