Metabolic flexibility and oxidative capacity independently predict insulin sensitivity in newly diagnosed patients with type 2 diabetes

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Background and aims:

Inherited and acquired insulin resistance have been related to abnormal muscle mitochondrial function. Mitochondrial function should be reflected by maximal oxygen uptake (VO_2max) and metabolic flexibility, defined as the difference between fasting and insulin-stimulated respiratory quotient (ΔRQ). However it is unclear, whether impaired ΔRQ results from impaired mitochondrial function or decreased glucose uptake due to insulin resistance. We hypothesized that VO_2max and ΔRQ correlate with each other and with insulin sensitivity and that gender, genetic variations associated with higher insulin sensitivity or VO_2max in peroxisome proliferator-activated receptors and cofactors (PPARγ, PPARδ, PGC-1α), NADH dehydrogenase 1 ß subcomplex 6 (NDUFB6) or ß-adrenergic receptor (ADRB) genes, glycemia or lipidemia would mediate such relationships.

Materials and methods:

A total of 121 patients (85 males, 36 females), all participants of the GDS, within the first year of type 2 diabetes (T2D) diagnosis were included. The patients underwent comprehensive phenotyping including hyperinsulinemic-euglycemic clamps, indirect calorimetry and cycling spiroergometry as well as genotyping for PPARγ, NDUFB6, PGC-1α, PPARδ and ADRB2 genes.

Results:

Males and females had comparable age (51±10 vs 52±11 years) but different body mass (BMI; 30.3±5.5 vs 33.8±7.6 $kg.m^{-2,}$ p=0.01) and VO_2max (29±5 vs 27±4 $ml.min^{-1}$.(kg fat free mass)$^{-1}$, p=0.05). Insulin sensitivity (M: 9.7(7.3,12.2) vs 9.7(7.1, 11.9) mg.(kg fat free mass)$^{-1}$.min^{-1}) and ΔRQ (0.11±0.06 vs 0.11±0.05, p=0.99) were nearly identical between males and females. ΔRQ and VO_2max did not correlate with each other, but both parameters associated with insulin sensitivity in both males and females (ΔRQ: males: β=1.91, p=0.002, females: β=2.46, p=0.014, VO_2max: males: β=0.04, p<0.0001, β=0.04 females: p=0.02). When we examined also the effect of body mass index, age, fat mass and waist-to-hip ratio performing multiple regression analysis, ΔRQ and VO_2max were remained independent predictors of insulin sensitivity in male (β=1.56, p=0.004 and β=0.02, p=0.006 respectively), but not in female participants. There was no association of the examined parameters with glycemic control, free fatty acids or tested gene variations.

Conclusion:

The absence of a relationship between VO_2max and ΔRQ despite their independent association with insulin sensitivity suggest that metabolic flexibility and oxidative capacity are different features of muscle mitochondrial function. Moreover, neither glycemia and lipidemia nor variants in genes related to oxidative metabolism affected the relationship between VO_2max and ΔRQ in T2D patients.