Higher fatty acids oxidation prevents intramyocellular lipid (IMCL) accretion and insulin resistance in humans with moderate increment of body fat mass.

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Introduction

Increment of body weight is supposed to impair insulin sensitivity and to increase the risk to develop type 2 diabetes. Usually increased body weight is associated to a detrimental lipid profile and recently abnormalities of lipid metabolism are considered important pathogenic events in obesity and type 2 diabetes [1]. In particular intra-myocellular triglyceride (IMCL) storage is considered a strong local marker of whole body insulin resistance and probably constitutes one of its crucial pathogenic factor. IMCL content has been difficult to measure in humans in the past because of the invasiveness of the biopsy procedure and because the concentration in the specimens may be confounded by contaminating adipose tissue along muscles in fasciae and in subcutaneous fat layers, which are not discernible from the intra-muscular pool using biochemical assay[2]. Using 1H NMR spectroscopy it was assessed a new method to measure separately lipids in fat cells and lipids located in the cytoplasm of muscle cells and recently the measurement of the intra-myocellular pool at 1.5 Tesla field strength was shown to be comparable in accuracy to biochemical measurement [3]. Aim of this study was to assess the effect of moderate increment of body fat content in young healthy subject on whole body insulin action, IMCL content, fatty acids oxidative disponsal and plasma free fatty acids concentrations in a cross-sectional fashion.

Methods

We selected 14 young (26±1 years), healthy, non-obese (BMI=21±1 kg/m2) women and 14 young (24±1 years), healthy, non-obese (BMI=24±1 kg/m2) men non exercising who had no family history of diabetes and additional diseases. To compare the effect of moderate increment of body fat on fatty acids metabolism and insulin action we studied women with a fat content >30% (n=7) and men >25% (n=7) and compared them one by one with subjects matched for age, gender and physical activity but with a fat content <30% in women and <25% in men. Within 2-3 days all the subjects underwent 1) localized 1H NMR spectroscopy of the calf muscles to assess IMCL content, 2) euglycemic-insulin clamp to assess whole body glucose metabolism, 3) indirect calorimetry to assess fatty acid oxidation, and 4) Dual energy X-ray absortion (DEXA) to assess body composition. 1H-NMR spectroscopy was performed on a GE Signa 1.5 Tesla scanner (General Electric Medical System, Milwaukee, WI) using a conventional linear extremity coil. Two 1H spectra were collected from a 15x15x15mm3 volume within the soleus and the anterior tibialis muscles, respectively. We used a PRESS pulse sequence (TR = 2000 msec, TE = 60 msec) and 128 averages were accumulated for each spectrum with a total acquisition time of 4.5 min. A third 1H spectrum of a triglycerides solution inside a glass sphere, positioned within the extremity coil next to the calf, was also obtained during the same session in order to have an external standard. The post processing of the data was executed with SAGE/IDL software (General Electric Medical System, Milwaukee, WI). The other techniques used in this study are described elsewhere [4].

Results

Subjetcs with higher body fat (32±1%) maintained similar insulin sensitivity (glucose disposal: 9.3±0.4 vs 9.5±0.5 mg/[kg LBM·min]; P=0.80), IMCL content in both soleus (62±7 vs 51±6 AU; P=0.22) and tibialis anterior (13±2 vs 12±2; P=0.75) muscles and plasma free-fatty acids levels (547±56 vs 404±56 μM; P=0.075) when compared to leaner subjects (body fat=18±2%) in association to increased fatty acids oxidative disposal (1.37±0.08 vs 1.17±0.05 mg/[kg LBM·min]; P<0.05), resting energy expenditure (REE: 36.1±1.1 vs 32.6±0.8 kcal//[kg LBM·day]; P=0.046), resting oxygen consumption (VO2: 5.14±0.16 vs 4.74±0.11 ml/[kg LBM·min]; P=0.049), and postabsorptive plasma leptin levels (8.04±1.30 vs 3.81±0.63 ng/ml; P<0.01). Leptin levels were strongly related to both VO2 (R2=0.36, P<0.001) and REE (R2=0.35, P=0.001).

Discussion

The results of this work might demonstrate that in healthy, young, sedentary subjects with no genetic background of diabetes or other diseases known to impair insulin sensitivity, the deleterious effects of moderately higher body fat content (>25% in men and >30% in women) on insulin sensitivity and fatty acids metabolism may be prevented by increased fatty acids oxidative disposal in the postabsorptive condition. To our knowledge this is the first report in which increased postabsorptive fatty acids oxidative disposal is associated to a beneficial effect on insulin action in healthy, sedentary humans.

Whole body insulin resistance was associated to increased IMCL content in normal subjects, offspring of type 2 diabetic parents, patients affected by type 2 diabetes and obesity and fatty acids are thought to induce insulin resistance by means of inhibition of insulin signaling. Skeletal muscle accretion of triglyceride in obesity might results from either increased fatty acids uptake or alternatively from diminished fat oxidation.

The findings of this study would support the hypothesis that IMCL accretion in condition of insulin resistance derives from reduced capacity for fatty acids oxidation. In fact, this study represents the reverse experiment in which subjects able to trigger the fatty acids oxidative disposal, developed an efficient compensatory mechanism to fight muscle fatty acids accumulation (driven by the higher fat availability) and consequently to avoid insulin resistance. In our opinion this study demonstrates that even in sedentary subjects the fatty acids oxidative pathway represents a crucial compensatory mechanism to fight insulin resistance and additional body weight gain in the early stages of the pathogenesis of obesity. In conclusion, moderate overweight subjects may maintain normal IMCL content and insulin sensitivity via increased fatty acids oxidative disposal; whether this compensatory mechanism is mediated by the increment of the leptin level is uncertain. This may suggest that 1) maintenance of normal IMCL content is crucial for preserving insulin sensitivity and 2) that inherited or acquired alterations of the ability of muscle (and eventually liver) to oxidize fatty acids represent predisposing factors for the development of abnormal IMCL accretion and in turn insulin resistance and obesity.

References

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