Abstract

Women with polycystic ovary syndrome (PCOS) have an increased risk of insulin resistance independent of bodyweight and the presence of hyperandrogenism is suggested to increase this risk. However, insulin resistance in lean women with PCOS is not universal and the underlying mechanism contributing to insulin resistance is poorly understood. As skeletal muscle is the main organ responsible for glucose uptake during hyperinsulinemia, the characterisation of skeletal muscle tissue from lean, hyperandrogenic women with PCOS might bring new insights into molecular mechanism that may be underlying insulin resistance in lean women with PCOS.

Whole body insulin sensitivity was determined and skeletal muscle biopsies were obtained in two separate groups of lean, hyperandrogenic women with PCOS and these were compared to matched control (CON) groups. When reviewing the literature, together with findings from study 1 and 2, it became evident that matching PCOS and CON subjects in regard to body mass index (BMI), age and cardiorespiratory fitness level is crucial when whole body insulin resistance is evaluated. Excluding these parameters might add to the divergent findings of insulin sensitivity in lean women with PCOS in the literature. Furthermore, a very sensitive and tightly regulated interplay between circulating levels of bioavailable testosterone, sex hormone-binding globulin (SHBG) and adiponectin appears to be linked to whole body insulin sensitivity. Accordantly, low circulating SHBG, high circulating free testosterone and low circulating adiponectin levels could potentially be important drivers of whole body insulin resistance in lean women with PCOS.

Whole body insulin resistance in lean women with PCOS was associated with abnormalities in skeletal muscle metabolism, which point to skeletal muscle as an important regulator of whole body insulin sensitivity in these women. Intramyocellular triglyceride (IMTG) and ceramide content were significantly higher in insulin resistant, lean women with PCOS than CON subjects but did not interfere with the proximal insulin signaling, which was comparable to CON subject. Thus, intramyocellular accumulation of IMTG and ceramide may not be important in the regulation of insulin action in lean women with PCOS. In contrast, reduced adenosine monophosphate (AMP)-activated protein kinase (AMPK) mediated signalling together with pyruvate dehydrogenase (PDH) dysregulation are possible molecular mechanisms in skeletal muscle contributing to insulin resistance in lean women with PCOS.
The effect of exercise training on insulin sensitivity and especially insulin-stimulated glucose uptake in skeletal muscle and endogenous glucose production was evaluated in lean, hyperandrogenic women with PCOS and healthy CON subjects. The subjects were matched for age, body mass index (BMI) and maximal oxygen uptake. A 14-week controlled and supervised exercise training intervention consisting of combined aerobic and strength training was completed. Women with PCOS did, in contrast to CON subjects, not increase whole body insulin sensitivity with the exercise training intervention. This was observed despite similar training intensity and improvements in cardiorespiratory fitness level in both groups. Insulin-stimulated glucose uptake in skeletal muscle was not improved in the PCOS group, as observed in the CON group. Biopsies obtained from the vastus lateralis muscle before and after the training intervention revealed that, in contrast to CON subjects, skeletal muscle glucose transporter 4 (GLUT4) and hexokinase II (HKII) protein and mRNA content together with activation of insulin stimulated signalling of Akt and Akt substrate of 160 kDa (AS160/TBC1D4) remained unaffected by exercise training in women with PCOS. Together, the data suggest the non-response in whole body insulin sensitivity in lean women with PCOS with training being caused by a lack of an increase in insulin-stimulated glucose uptake in skeletal muscle and this appeared to be due to an absence of training-induced increase in key metabolic proteins and insulin signalling in skeletal muscle.