

**Assessing the effects of dehydroepiandrosterone replacement on insulin sensitivity and skeletal muscle physiology in hypoadrenal women**

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Dehydroepiandrosterone (DHEA) and its sulfated ester (DHEAS) are the most abundant circulating steroid hormones. Their physiological function has yet to be determined. Hypoadrenal subjects lack this hormone because DHEA replacement is not part of the current standard of care. There are conflicting reports on the impact of DHEA replacement in hypoadrenal subjects on insulin sensitivity.

We aimed to test this hypothesis and examine skeletal muscle physiology using a hyperinsulinaemic euglycaemic clamp after 12 weeks of DHEA and placebo in a cross over study.

In a randomized, double-blind, placebo controlled, cross over study, 33 hypoadrenal women ( $\pm$ SD) (mean age  $49.7 \pm 15.6$  years) received either a single daily dose of 50mg of DHEA or placebo. After 12 weeks body composition was assessed by DEXA and insulin sensitivity was assessed.

There were no differences in body composition. Fasting plasma insulin and glucagon were lower with DHEA ( $7.07 \pm 4.35$  vs  $8.88 \pm 5.81$  microU/ml,  $p=0.003$  and  $177.7 \pm 59.9$  vs  $195.04 \pm 79.5$  pg/ml,  $p=0.038$  respectively). There was a strong trend to lowering fasting glucose on DHEA ( $4.67 \pm 0.54$  vs  $4.83 \pm 0.58$  mmol/l,  $p=0.054$ ).

Despite comparable glucose levels during the clamps, plasma insulin and plasma glucagon levels were significantly lower after 12 weeks of DHEA supplementation ( $7.07 \pm 4.35$  vs  $8.88 \pm 5.81$  microU/ml,  $p=0.003$  and  $51.06 \pm 17.2$  vs  $56.03 \pm 22.85$ ,  $p=0.038$  respectively). The amount of glucose infused during the hyperinsulinemic clamp was higher for DHEA ( $1.34 \pm 0.53$  vs  $1.22 \pm 0.52$  mg.min<sup>-1</sup>.KgFFM<sup>-1</sup>,  $p=0.02$ ). GLUT 4 mRNA levels did not change with DHEA when normalized for 28S ( $2.467 \pm 2.91$  vs  $2.99 \pm 3.33$  units,  $p=0.62$ ).

DHEA use also resulted in significant reductions in total cholesterol, ( $4.62 \pm 0.9$  vs  $5.23 \pm 0.83$  mmol/l,  $p=0.007$ ), triglycerides, ( $1.52 \pm 0.7$  vs  $1.70 \pm 0.80$  mmol/l,  $p=0.016$ ), and HDL cholesterol, ( $0.97 \pm 0.32$  vs  $1.09 \pm 0.33$  mmol/l,  $p=0.003$ ).

This study shows that 50mg of DHEA significantly increased insulin-mediated glucose disposal in hypoadrenal women. Whilst the TC/HDL ratios were unchanged, the effects on triglycerides may explain the epidemiological

observations correlating reduced cardiovascular mortality with high DHEA levels.

The need for DHEA replacement in hypoadrenal women warrants further attention

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