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Suppressed osteocalcin and muscle protein signalling mediate glucocorticoid-induced basal and post-exercise insulin resistance in humans

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Background. Glucocorticoids (GC) are used for the treatment of inflammatory and autoimmune conditions but lead to the development of insulin resistance. In mice, GC-induced insulin resistance occurs primarily through impaired osteoblast function and uncarboxylated osteocalcin (ucOC) secretion, however, this has yet to be established in humans. Furthermore, acute exercise increases ucOC secretion and insulin sensitivity, however the effects of GC on post-exercise glycaemic control and ucOC secretion are unknown. We investigated the effect of GC on basal and post-exercise insulin sensitivity, ucOC secretion, and insulin signalling.

Methods. In a randomised, crossover, double-blind study, nine healthy males (Age: 28 ± 2 years; BMI: 24 ± 1; Mean ± SEM) completed two separate cycling sessions 12 hours after ingesting either GC (20 mg prednisolone) or placebo. The homeostatic model assessment was used to assess basal insulin resistance and a 2-hour euglycaemic-hyperinsulinaemic clamp was commenced 3 hours after exercise to assess insulin sensitivity.

Results. Compared with placebo, GC decreased serum ucOC (-24%, $P<0.01$), which was associated with decreased basal (-47±5%, r=0.54, $P<0.01$) and post-exercise insulin sensitivity (-34±5%, r=0.72, $P<0.01$). GC decreased skeletal muscle protein abundance of the ucOC receptor (GPRC6A: -16%, $P<0.05$) and attenuated the post-exercise insulin-stimulated phosphorylation of glucose uptake signalling proteins $mTOR^{Ser2481}$, Akt^{Ser374} and $AS160^{Thr642}$ (-59%, -61% and -50%, respectively; $P<0.05$). Attenuated mTOR, Akt and AS160 signalling correlated with lower ucOC (r=0.61-0.71, $P<0.05$) and lower post-exercise insulin sensitivity (r=0.54-0.75; $P<0.05$).

Conclusion. GC-induced basal and post-exercise insulin resistance in humans is linked to the suppression of ucOC secretion and signalling. Targeting ucOC may be a novel approach for improving glycaemic control in populations who are insulin resistant and/or undergoing GC therapy.

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