61 | Glucocorticoid induced suppression of osteocalcin is associated with attenuated post-exercise insulin sensitivity and impaired skeletal muscle mTOR and insulin signaling in humans

Lewan Parker[1]; Andrew Garnham[2]; Glenn McConell[1]; Nigel Stepto[1]; David Hare[3]; Elizabeth Byrnes[4]; Peter Ebeling[5]; Ego Seeman[6]; Tara Brennan-Speranza[7]; Itamar Levinger[1]

[1]Institute of Sport, Exercise and Active Living, Victoria University, Melbourne, Vic., Australia; [2]School of Exercise & Nutrition Sciences, Deakin University, Melbourne, Vic., Australia; [3]University of Melbourne and the Department of Cardiology, Austin Health, Melbourne, Vic., Australia; [4]PathWest QEII Medical Centre, Perth, WA, Australia; [5]Department of Medicine, School of Clinical Sciences, Monash University, Melbourne, Vic., Australia; [6]Department of Endocrinology, University of Melbourne and Austin Health, Melbourne, Vic., Australia; [7]Department of Physiology, University of Sydney, Sydney, NSW, Australia

Purpose: Glucocorticoid (GC) treatment impairs osteoblast function, undercarboxylated osteocalcin (ucOC), and insulin sensitivity. However, the effects of acute GC ingestion on post-exercise insulin sensitivity in humans are unclear. We investigated whether the suppression of ucOC, by a single dose of GC (prednisolone), would be associated with impaired post-exercise insulin sensitivity and skeletal muscle mTOR/insulin protein signalling.

Methods: Nine healthy males (Age: 28 ± 2 years; BMI: 24 ± 1; Mean ± SEM) were randomly allocated in a double-blinded crossover design to ingest a single dose of prednisolone (20 mg) and placebo, ~7 days between trials. Twelve hours after capsule ingestion, after an overnight fast, participants performed a session of high-intensity interval exercise (4 × 4-minute cycling intervals at 90%-95% HR_{peak}, 2-minute active recovery periods). The homeostatic model assessment (HOMA2-IR) was used to assess resting insulin resistance and the euglycaemic-hyperinsulinaemic clamp (EHC) was used to assess insulin sensitivity 5 hours after exercise. Serum ucOC, and skeletal muscle $AS160^{Thr642}$, Akt^{Ser473} and $mTOR^{Ser2481}$ protein phosphorylation, were measured at baseline and post-EHC.

Results: Compared to placebo, prednisolone treatment suppressed ucOC at baseline (−24 ± 2%, $P < .001$) and post-EHC (−18 ± 2%), which coincided with increased HOMA2-IR (107 ± 27%, $P < .001$) and decreased post-exercise insulin sensitivity (−34 ± 5%, $P < .001$). Higher serum ucOC was associated with lower HOMA2-IR ($r = -.54$, $P < .05$) and greater post-exercise insulin sensitivity ($r = .72$, $P < .01$). Prednisolone significantly impaired ($P < .05$) the post-exercise insulin stimulated increase in skeletal muscle $AS160^{Thr642}$ (~−50%), Akt^{Ser473} (~−61%) and $mTOR^{Ser2481}$ (~−59%) phosphorylation, which significantly correlated ($P < .01$) with lower serum ucOC ($r = .64$, $r = .71$ and $r = .61$, respectively) and post-exercise insulin sensitivity ($r = .56$, $r = .75$, $r = .54$, respectively).

Conclusions: The negative effect of prednisolone on insulin sensitivity at rest and following exercise are related, at least in part, to the suppression of ucOC and mTOR/insulin signalling. Targeting ucOC mediated signalling pathways in humans may prove to be an effective intervention for improving glycaemic control in insulin resistant populations.

62 | Cyproterone vs spironolactone as anti-androgen therapy for transgender females receiving oestradiol therapy

Ada S. Cheung[1]; Olivia Ooi[1]; Dahlia Davidoff[1]; Shalem Y. Leemaqz[2]; Pauline Cundill[3]; Nicholas Silberstein[3]; Ingrid Bretherton[1]; Mathis Grossmann[1]; Jeffrey D. Zajac[1]

[1]Department of Medicine (Austin Health), The University of Melbourne, Heidelberg, Vic., Australia; [2]Adelaide Medical School, The University of Adelaide, Adelaide, South Australia; [3]Victorian AIDS Council, Equinox Clinic, Fitzroy, Victoria

Background: Feminising cross-sex hormone therapy improves psychological functioning in male-to-female individuals with gender dysphoria. Oestradiol with or without an antiandrogen (cyproterone acetate or spironolactone) are commonly prescribed in those without orchidectomy. Guidelines for treatment are based on poor quality evidence. We aimed to compare add-on cyproterone versus spironolactone in lowering endogenous testosterone levels in male-to-female transgender individuals.

Methods: A cross-sectional analysis was performed of 114 trans and gender diverse individuals receiving (1) oestradiol alone (n = 21), (*2) oestradiol plus cyproterone (n = 21), or (3) oestradiol plus spironolactone (n = 38) for >6 months. We excluded those on GnRH agonists (n = 1), previous orchidectomy (n = 28), and ethinyloestradiol treatment (n = 4) as this was not measurable on our oestradiol immunoassay. Total testosterone level (radioimmunoassay) and secondary outcomes included oestradiol level, oestradiol valerate (Progynova™) dose, blood pressure and renal function. Median (IQR) are reported and differences were tested using Kruskal-Wallis test followed by Nemenyi post-hoc comparisons. A linear mixed model was also fitted with recruiting centre as random effect.

Results: Eighty-one individuals (27.0 years (22.5, 45.1)) were included. Median duration of hormone therapy was 1.5 years (0.9, 2.6). On univariate and multivariable analyses, the cyproterone group had significantly lower total testosterone levels (0.8 nmol/L (0.6, 1.20), n = 21) compared with spironolactone group (2.0 nmol/L (0.9, 9.4), $P = .037$, n = 38) and oestradiol alone (10.5 nmol/L (4.9, 17.2), $P < .001$, n = 21). No differences were observed in oestradiol level, total daily Progynova™ dose, body mass index, blood pressure, haemoglobin, creatinine, potassium or ALT. Urea was higher in the spironolactone group compared with cyproterone. Median dose of spironolactone was 100 mg (87.5, 200), and cyproterone 50 mg (25, 50).

Conclusions: Oestradiol plus cyproterone achieved total testosterone levels in the female reference range. As spironolactone may cause feminisation without inhibition of steroidogenesis, it is unclear which anti-androgen is more effective at feminisation. Further prospective studies are required.