Society for Endocrinology media release

For immediate release

Balancing between too much testosterone and too much steroid: new data on health outcomes in adults with congenital hormone disorder

New research provides insights into treatment options for the commonest inherited hormonal deficiency, congenital adrenal hyperplasia (CAH), affecting an estimated 3,600 adults in the UK. The study by researchers from across the UK, published in *Clinical Endocrinology*, indicates that higher doses of medication in patients with CAH does not improve disease control and may be associated with side effects.

CAH is an inherited condition that results from a deficiency of the stress hormone steroid cortisol. This causes an over-production of male hormones known as androgens (such as testosterone) and as a consequence patients suffer from problems with growth, gender-related development in females, and fertility. To counteract this, patients are prescribed daily steroid medication to replace the cortisol and suppress the androgens. From the clinician's perspective this provides a delicate balancing act between too little steroid and high androgens and too much steroid and steroid-related side effects. The study's aim was to investigate how the type and dose of steroid replacement might be related to health and metabolic outcomes.

The Society for Endocrinology formed the Congenital adrenal Hyperplasia Adult Study Executive (CaHASE) to collate data on consenting adults with CAH from centres across the UK, with the aim of forming a consensus for management of the condition in adulthood. 196 men and women with CAH were given a physical examination (blood pressure, height, weight) and a biochemical assessment (for metabolic parameters influenced by steroid treatment such as insulin resistance, cholesterol, triglycerides and androgens). Patients had their medications noted and were grouped by the severity of their disease (by genotype).

Patients taking the potent steroid dexamethasone had lower androgen levels but were also more insulin resistant and patients taking a single dose per day or higher doses of dexamethasone were significantly more likely to be insulin resistant.

After accounting for age and sex, a computational method called principal components analysis was used to identify trends in health outcomes related to the medication. As patients were on different types of steroid replacement their 'equivalent dose' was calculated via three different published formulae[2,3,4]. This analysis identified two areas that were significantly and positively related to medication dose ($p<0.05$): *disease control* (increased dose is associated with increased levels of androgens in the blood) and *blood pressure and mutation severity* (increased dose is associated with increased blood pressure and more severe mutations). The results indicated that higher medication doses do not correspond to better disease control (lower androgens), but do correspond to raised blood pressure and to more severe genetic defects known as mutations.

The data show that dexamethasone gave better disease control but also increased signs of steroid excess (insulin resistance), and that higher doses of steroid medication actually correlated with worse disease control, and may adversely affect health. The data should inform further research into this condition and provide further motivation for doctors to refer all adults with CAH to specialist endocrine centres for multidisciplinary assessment and treatment.

Professor Richard Ross of the Society for Endocrinology and Chairman of the Congenital adrenal Hyperplasia Adult Study Executive (CaHASE) said:
"There is currently no consensus on the best treatment to manage congenital adrenal hyperplasia in adults.

"We prescribe steroids to replace cortisol and suppress testosterone. We found that patients on dexamethasone showed higher risk of insulin resistance, particularly in high, once daily doses. Our results also show that patients on the highest doses of steroids also seem to have the highest levels of testosterone. The risks of steroid excess include high blood pressure and obesity, and the data show these effects in many of our patients.

"We would recommend that doctors think before increasing the steroid dose, as this may only increase side effects. We also suggest that dexamethasone is only used in those patients that desire strong androgen suppression. Finally, we would recommend that all adults with CAH are referred to specialist endocrine centres for specialist care."

Information on congenital adrenal hyperplasia
CAH is an inherited disorder resulting from a defect in the adrenal enzyme responsible for synthesis of the stress steroid cortisol. The body senses that no cortisol is being produced and signals to the adrenal glands to produce cortisol. As the adrenals cannot produce cortisol an excess of precursor steroids that are predominantly androgens builds up and is released into the bloodstream. The over-production of androgens (male hormones; predominantly testosterone) in CAH means that girls with CAH can develop ambiguous genitalia during foetal development, and unless treated from birth they become virilised, developing a male pattern of body and facial hair (hirsutism). Boys and girls can enter a very early 'precocious' puberty. In both sexes growth and fertility problems are common. Much less is known about the condition in adulthood, but inadequate treatment results in infertility in both sexes, and as the natural daily pattern of cortisol levels is hard to mimic with current medication long-term excess treatment can result in adverse effects such as high blood pressure and obesity.

---------Ends--------

Notes for editors:
This research is published in the Jan 2013 issue of *Clinical Endocrinology* **78**; 197-203, DOI: 10.1111/cen.12045 (Open Access).

The Society for Endocrinology is UK's largest national organisation promoting endocrinology and hormone awareness. For general information, please visit our website: www.endocrinology.org

'Living with CAH' is a patient group that works to improve the medical management of CAH and offers information and support on CAH to patients and their friends and family: http://www.livingwithcah.com/.

References:
[1] Arlt et al. 2010. *J Clin Endocrinol Metab*, **95,** 5110-5121.
[2] British National Formulary (BNF **63**) 2012.
[3] Rivkees SA, Crawford JD. *Pediatrics* 2000; **106**:767-73.
[4] Arlt W. *J Clin Endocrinol Metab* 2009; **94**:1059-67.

Please mention the Society for Endocrinology in any story

For more information: please contact the Society for Endocrinology press office

Toby Stead
Public & Media Relations Executive
Tel: +44 (0)1454 642 252
Email: toby.stead@endocrinology.org

Paul MacKenzie-Cummins
Communications and Public Relations Manager
Mob: +44(0)7453 755 057
Tel: +44 (0)1454 642 772
Email: paul.mackenzie-cummins@endocrinology.org

ABSTRACT

Glucocorticoid treatment regimen and health outcomes in adults with congenital adrenal hyperplasia

Han TS[1], Stimson RH[2], Rees DA[3], Krone N[4], Willis DS[5], Conway GS[1], Arlt W[4], Walker BR[2], Ross RJ[6] and the United Kingdom Congenital adrenal Hyperplasia Adult Study Executive (CaHASE).*

[1] Department of Endocrinology, University College London Hospitals; [2] Queen's Medical Research Institute, University of Edinburgh [3] Centre for Endocrine and Diabetes Sciences, Cardiff University [4] Centre for Endocrinology, Diabetes and Metabolism, University of Birmingham[5] Society for Endocrinology [6] Academic Unit of Diabetes, Endocrinology & Metabolism, University of Sheffield

Background
Adults with congenital adrenal hyperplasia (CAH) are treated with a wide variety of glucocorticoid treatment regimens.

Objective, design and methods
To test whether drug dose and timing of glucocorticoid treatment regimen impacts on health outcomes. This was a cross-sectional study of 196 adult CAH patients in whom treatment and health outcomes were measured. Glucocorticoid dose was converted to prednisolone dose equivalent (PreDEq) using three published formulae. Associations between the type of glucocorticoid regimen or PreDEq with specific health outcome variables were tested using partial correlation and principal components analysis (PCA).

Results
Patients on dexamethasone had lower androgens and ACTH but greater insulin resistance compared to those receiving hydrocortisone or prednisolone. Dexamethasone dose and once daily administration were associated with insulin resistance. Partial correlation analysis adjusted for age and sex showed PreDEq weakly correlated (r <0.2) with blood pressure and androstenedione. Mutation severity was associated with increased PreDEq ($F_{3,141}$ = 4.4, P<0.01). In PCA, 3 PCs were identified that explained 62% of the total variance (r^2) in observed variables. Regression analysis (age and sex adjusted) confirmed that PC2, reflecting *disease control* (androstenedione, 17-hydroxypregesterone and testosterone), and PC3, reflecting *blood pressure and mutations* (systolic and diastolic blood pressure and mutation severity), related directly to PreDEq (r^2 = 23%, P<0.001).

Conclusions
In adults with CAH, dexamethasone use was associated with lower androgens but greater insulin resistance, and increasing glucocorticoid dose associated with increased blood pressure, poor disease control and mutation severity.