Mapping the Steroid Response to Major Trauma From Injury to Recovery: A Prospective Cohort Study

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Context: Survival rates after severe injury are improving, but complication rates and outcomes are variable.

Objective: This cohort study addressed the lack of longitudinal data on the steroid response to major trauma and during recovery.

Design: We undertook a prospective, observational cohort study from time of injury to 6 months postinjury at a major UK trauma centre and a military rehabilitation unit, studying patients within 24 hours of major trauma (estimated New Injury Severity Score (NISS) > 15).

Main outcome measures: We measured adrenal and gonadal steroids in serum and 24-hour urine by mass spectrometry, assessed muscle loss by ultrasound and nitrogen excretion, and recorded clinical outcomes (ventilator days, length of hospital stay, opioid use, incidence of organ dysfunction, and sepsis); results were analyzed by generalized mixed-effect linear models.

Findings: We screened 996 multiple injured adults, approached 106, and recruited 95 eligible patients; 87 survived. We analyzed all male survivors <50 years not treated with steroids (N = 60; median age 27 [interquartile range 24–31] years; median NISS 34 [29–44]). Urinary nitrogen excretion and muscle loss peaked after 1 and 6 weeks, respectively. Serum testosterone, dehydroepiandrosterone, and dehydroepiandrosterone sulfate decreased immediately after trauma and took 2, 4, and more than 6 months, respectively, to recover; opioid treatment

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Over 5 million people worldwide die each year from serious injury (1), with almost 25% caused by road traffic collisions (RTC) (2). In England alone, there are 5400 trauma deaths and 20 000 severe injuries treated by the National Health Service annually (3). Since 2012, the establishment of 22 trauma centers in England has been accompanied by a 19% improvement in survival odds following injury (4). During this time, the United Kingdom also received severely injured military trauma patients from the conflict in Afghanistan (5).

Improvements in short-term outcomes have been achieved through early resuscitation and acute care (6), often informed by approaches pioneered on the battlefield. However, improvement in survival is often offset during the weeks following acute major trauma by the systemic inflammatory response syndrome (SIRS), which is associated with increased risks of infection, multiorgan dysfunction or failure (MOD/MOF), and death (7, 8). Simultaneously, the hypothalamic-pituitary-adrenal axis (HPA) is thought to drive a hypermetabolic and overtly catabolic response. Importantly, in this profound catabolic state, patients lose valuable lean muscle and suffer from increased rates of infection and poor wound healing. Moreover, the dynamic nature of this response, especially beyond the first few days following injury and during recovery, remains poorly described and understood, limiting the evidence base for novel therapeutic interventions. Burn injury also produces an extreme inflammatory and catabolic response after injury, previously targeted by anabolic steroid analogues (9) and beta-blockade (10). The dynamic changes in endogenous glucocorticoids and their influence on adrenal steroid metabolism after severe injury are not well characterized. We know that proinflammatory cytokines activate the enzyme 11β-hydroxysteroid dehydrogenase type (11β-HSD1) responsible for tissue-specific activation of glucocorticoids through the conversion of inactive cortisone to active cortisol (11). However, only scarce data exist on what happens to early sex steroids and their precursors during this catabolic state.

To address these gaps in knowledge, we have undertaken a detailed prospective study of the endocrine and metabolic response to severe injury in military and civilian populations, recruiting patients within 24 hours of major trauma and following up for the 6 months post-trauma. This was undertaken to identify predictive biomarkers and therapeutic targets as well as to explore the optimal timing for therapeutic interventions that could promote better recovery after severe traumatic injury.

**Materials and Methods**

**Study design and protocol**

This prospective cohort study was conducted in the Royal Centre for Defense Medicine and the Queen Elizabeth Hospital Birmingham, a major UK trauma center and the primary receiving facility for UK military personnel injured abroad. Military and civilian trauma patients with an estimated New Injury Severity Score (NISS) >15 were recruited (12). The NISS was used to ensure those with significant extremity trauma but lower injury severity score were included (13). Patients with significant head injury or preinjury neoplastic conditions were not eligible. None of the patients received etomidate during their treatment. Informed consent was obtained from personal consultees until recovering capacity. The protocol was approved by the NRES Committee South West – Frenchay 11/ SW/0177 and MOD REC 116/Gen/10.

A daily patient review allowed the injured to be clinically phenotyped. Bespoke study management software (Clinical RESearch Tool – CREST) tracked the patient and their clinical data were entered prospectively and used to calculate an Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), and Simplified Acute Physiology Score (SAPS) (14, 15). Sepsis was defined using Bone’s criteria of an infection associated with SIRS (16), current at the time of the study.

Details of opioid administration were collected from the electronic health record and prescribing system (PICS) (17) on each of the study patients. The total amount of opioid given during their hospital stay was appropriately weighted and totaled with equivalence to an oral dose of 10 mg morphine, adjusting for potency, delivery method, and opioid preparation (18).

Blood and urine samples were collected within 24 hours of acute injury and at 3, 5, 10, 14, 21, 28 days and 2, 3, 4, and 6 months during recovery post-trauma. Blood sampling occurred between 7:30 AM and 9:00 AM; serum was then separated and frozen at -80°C for batched analysis. We separately collected morning blood samples from 37 healthy age- and sex-matched controls, to provide a comparator for the steroid data.

**Assessment of protein catabolism**

As a surrogate marker for muscle mass, we undertook longitudinal measurements of muscle thickness by a well-validated method using portable ultrasound as described by Campbell et al (19, 20). Ultrasound measurements were taken from 4 different
Results

Patient recruitment and clinical characteristics of the final study cohort

We screened 996 multiply injured adults. The majority of the 889 excluded patients had a NISS ≤ 15, others had a significant head injury as their major injury component, and 2 were excluded due to a preinjury diagnosis of cancer. Of the 102 patients recruited into the study, 2 withdrew, and reassessment in 5 revealed an actual NISS ≤ 15, leaving a study cohort of 95 patients (Fig. 1A).

Excluding 8 fatalities and 7 patients who had received steroid therapy, 80 survivors completed sample collection over 6 months. To minimize confounders, we excluded the small groups of women (n = 9) and age-advanced men (n = 11), leaving our final study cohort of 60 men <50 years of age (Fig. 1B).

A summary of the cohort characteristics is shown in Fig. 2. Median age was 27 (interquartile range [IQR] 24–31) years, median NISS was 34 (IQR 29–44), and patient day-1 (= day of major trauma) APACHE II score was 21 (IQR 14–25). Patients remained ventilated on the intensive care unit (ICU) for a median of 9 (IQR 5–16) days. Median length of hospital stay was 36 (IQR 19–56) days. Improvised explosive device (IED) (n = 33; 55%) and RTC (n = 11; 18%) were the most common causes of injury. Twenty-five (42%) patients had at least 1 septic episode and most occurred in the second week (Fig. 2C).

Glucocorticoid biosynthesis and metabolism after major trauma

Serum cortisol concentrations increased slightly after injury, peaking at 408 (IQR 249–511) nmol/L at 2 weeks (Fig. 3A) (33). However, concentrations remained within the wide range observed in healthy controls. Serum concentrations of the inactive glucocorticoid metabolite cortisone were lower than normal after injury, and increased slowly over time, but this trend was not significant (P = 0.08) (Fig. 3B) (33).

The serum cortisol-to-cortisone ratio, a marker of systemic 11β-HSD activities (Fig. 3C), peaked at 2 weeks postinjury and returned to normal at around 8 weeks. Consistent with these findings, urinary steroid metabolite excretion analysis revealed an increase in glucocorticoid metabolite excretion in weeks 2, 4, and 8 after major trauma, alongside changes in steroid metabolite ratios indicative of increased systemic 11β-HSD1 and decreased 11β-HSD2 activities, as assessed by (5α-tetrahydrocortisol + tetrahydrocortisol)/tetrahydrocortisone and cortisol-to-cortisone ratio, respectively (33).

Androgen biosynthesis and activation after major trauma

Serum concentrations of the adrenal androgen precursor dehydroepiandrosterone (DHEA) were very low after injury (P < 0.0001, compared with healthy controls) but recovered to the normal range by 3 months
Within the healthy reference range, even at the end of the 6-month study period (Fig. 3E). Consequently, the serum DHEA-to-DHEAS ratio (Fig. 3F) increased by postinjury (Fig. 3D) (33). In contrast, its sulfate ester, DHEAS, demonstrated sustained suppression; median serum DHEAS concentrations did not recover to values within the healthy reference range, even at the end of the 6-month study period (Fig. 3E). Consequently, the serum DHEA-to-DHEAS ratio (Fig. 3F) increased by
week 2 compared with controls and failed to return to normal during the 6-month study period. The serum cortisol-to-DHEAS ratio (Fig. 3G) increased postinjury, peaking at 2 weeks, followed by a gradual decrease, but without returning to normal by the end of the 6-month study period.

Serum concentrations of the androgen precursor androstenedione (Fig. 3H) were below the reference range immediately after injury, recovering to the midreference range at 2 weeks postinjury. Thus, serum androstenedione concentrations recovered much faster than DHEA, suggestive of rapid downstream activation of DHEA to androstenedione.

Serum testosterone (Fig. 3I) (33) was very low following injury, starting to increase after 2 weeks, and recovering to the healthy sex- and age-matched reference range approximately 8 weeks after injury. This was mirrored by acute suppression of serum LH immediately after injury, followed by recovery to the normal range approximately 2 weeks after injury (33). Serum sex hormone-binding globulin (SHBG) (33) concentrations were subnormal immediately postinjury, but quickly returned to the healthy reference range between injury and day 7.

Consistent with the observed decrease in circulating androgens, 24-hour urinary steroid metabolite excretion...
analysis revealed a steep decrease in the major androgen metabolites androsterone and etiocholanolone at 2, 4, and 8 weeks (33). Similarly, urinary DHEA excretion, representing the sum of unconjugated DHEA and DHEA sulfate, sharply decreased to very low concentrations at 2, 4, and 8 weeks, with a transient increase in 16α-hydroxylation of DHEA at 2 weeks (33), possibly linked to the systemic decrease in DHEA sulfation (Fig. 3D–F). The overall decrease in androgen production was paralleled by a profound decrease in systemic 5α-reductase activity (33), and hence in androgen activation, as 5α-reductase is responsible for converting testosterone to the most potent androgen 5α-dihydrotestosterone.

**Protein catabolism after major trauma**

The 24-hour TUN excretion increased immediately after trauma, peaking at 25.0 ± 16.1 g/day at the end of the first week, returning to below 15.0 g/day by week 4. The mean maximum rate of nitrogen excretion was 33.0 ± 21.3 g/day (Fig. 4A). The normalization of TUN excretion coincided with the gradual recovery of adrenal and gonadal androgen production (Fig. 4B and 4C).

The biceps brachii muscle was the most reliable site for ultrasound measurement of muscle thickness; dressings, amputations, and other wounds hampered the measurements of the other muscle areas. Changes in biceps brachii muscle thickness followed a U-shaped curve after injury, reaching a nadir at 6 weeks (day-1 after trauma compared with week 6, \( P = 0.001 \)). The mean muscle loss was 22.7 ± 12.5% (Fig. 4D). Similar to TUN, muscle thickness recovered alongside gradually increasing adrenal and gonadal androgen production (Fig. 4E and 4F).

**Clinical course of post-traumatic recovery and serum androgen dynamics**

The relationship between adrenal and gonadal androgens and the Sequential Organ Failure Score (SOFA) and probability of sepsis are illustrated in Fig. 5. During the first 4 weeks, serum DHEA, DHEAS, and testosterone all correlated with the clinical SOFA score (autocorrelation factor [ACF] = 0.85, 0.90, and -0.79, respectively). The serum concentrations of all 3 steroids also showed strong associations with the probability of sepsis (\( R = -0.85 \), 0.85, and -0.97 for serum DHEA, DHEAS, and...
testosterone, respectively). The SOFA score and probability of sepsis also correlated strongly with the DHEA:DHEAS ratio (ACF = -0.94 and -0.96, respectively) and with the serum cortisol-to-DHEAS ratio, negatively for the SOFA score but positively for probability of sepsis (ACF = -0.81 and 0.89, respectively) (33).

Opioid administration and endocrine recovery

To examine whether opioid administration affected endocrine recovery, we modeled the impact of the total cumulative in-patient opioid dose on circulating steroid concentrations during recovery from major trauma. For this purpose, we categorized patients according to cumulative opioid dose. Modeling took into account the differences in injury severity score, length-of-stay (LOS), ICU LOS, and SOFA score.

The adjusted modeling revealed a dose-dependent impact of opioid treatment, with a higher initial peak of serum cortisol and the cortisol/cortisone ratio in those on higher doses (≥3000 mg), while those on lower doses had initially lower serum cortisol concentrations but showed better recovery of cortisol and cortisol/cortisone 2 months into the recovery period, with broad interindividual variability in those with high cumulative opioid doses (Fig. 6).

Opioid administration showed a pronounced, dose-dependent effect on adrenal and gonadal androgen production, with significantly delayed recovery of serum DHEA and DHEAS in patients on higher opioid doses.

Figure 5. Sequential Organ Failure Assessment (SOFA) score and probability of sepsis in relation to endocrine response. The SOFA and sepsis are related serum concentrations of DHEA (A and B), DHEAS (C and D), and testosterone (E and F). Data were modeled using a nonlinear mixed effects model that accounts for unbalanced repeated measures using a 4-knot cubic spline. Modeled data are reported as means and 95% confidence intervals.
($P = 0.029$, $P < 0.001$, respectively; Fig. 7). By contrast, serum testosterone concentrations, which were initially equally suppressed in all cumulative dose groups, showed a much faster recovery in individuals who received higher ($\geq 3000$ mg) total cumulative opioid doses. However, these confidence intervals were large for these model estimates (Fig. 7).

**Discussion**

In this study, we have characterized the response of adrenal and gonadal steroids and catabolic metabolism to severe injury, describing the related dynamic changes for 6 months postinjury. Modeling the data has allowed us to provide a detailed description of the transition from catabolism to anabolism during recovery from severe injury, including investigating the impact of cumulative in-patient opioid dose. Our data are the first to provide detailed adrenal and gonadal steroids beyond the first days after trauma in a large cohort of young patients, with all patients recruited prospectively and steroid analysis carried out by tandem mass spectrometry.

As summarized in a recent meta-analysis (34), previous data on serum cortisol after injury are limited to small cohorts derived from elective surgery, rarely followed-up for more than 2 days. In our study, serum cortisol quickly returned to normal following slight initial increases after acute trauma. In contrast, serum cortisone remained low for 3 months postinjury. Our study revealed an initial phase of minor glucocorticoid activation with a transient increase in the serum cortisol-to-cortisone ratio, with changes in urinary glucocorticoid metabolites indicative of increased 11$\beta$-HSD1 activity. The cortisol-activating enzyme 11$\beta$-HSD1 is the major enzyme converting inactive cortisone to cortisol and has been shown to be upregulated systemically and locally.

![Figure 6](https://academic.oup.com/jcem/article-abstract/105/3/dgz302/5758226)
in response to inflammation, thereby dampening the inflammatory response (35, 36). Skeletal muscle expresses 11\(\beta\)-HSD1 (37). Previous studies reported increased 11\(\beta\)-HSD1 activity in an animal model of trauma haemorrhage (38) and improved wound healing in mice treated with 11\(\beta\)-HSD1 inhibitors (39). However, human data after trauma are lacking. There is substantial evidence indicating a reduced cortisol clearance in critical illness, due to decreased cortisol inactivation in liver and kidney (40); this mechanism could also be responsible for the slight changes in cortisol and cortisone we observed. This was corroborated by the observed reduction in the urinary cortisol-to-cortisone ratio, which is reflective of 11\(\beta\)-HSD2 activity.

Interestingly, patients on higher opioid doses showed a higher early peak in cortisol production after trauma, followed by persistently lower circulating cortisol during the recovery period, as compared with patients on lower opioid doses. Previous reports have described suppressive effects of opioids on the HPA axis, though studies in smaller mammals have indicated an acute stimulatory effect of opioid administration on serum cortisol concentrations (41, 42).

We observed a pronounced and sustained loss of adrenal and gonadal androgen synthesis within the first 24 hours following acute major trauma. The recovery of circulating DHEA and testosterone concentrations took 2 and 4 months postinjury, respectively, and DHEAS remained pathologically suppressed at the end of the 6-month follow-up period. In a mouse model of acute inflammation, sustained suppression of the expression of the DHEA sulfotransferase SULT2A1 and its sulfate donor enzyme, PAPSS2, have been described (43). We reviewed 23 previous studies that measured serum DHEA and DHEAS in critically ill patients (33, 44), but most studies followed patients...
for only a few days and relatively few patients suffered from acute trauma. One previous study measured both serum DHEA and DHEAS in 181 patients with septic shock and 31 patients with acute hip fracture (45). Serum DHEAS was decreased in both groups, while DHEA was increased in sepsis but decreased after trauma. This suggested an inflammation-mediated downregulation of DHEA sulfation after trauma, resulting in a dissociation of serum DHEA and DHEAS. In our study, this was also observed, as indicated by a sustained increase in the serum DHEA/DHEAS ratio and persistently low serum DHEA concentrations.

A number of previous studies have described an association between infection and mortality with low circulating DHEAS concentrations and a raised serum cortisol-to-DHEAS ratio in patients with trauma (46–49). In vitro studies have demonstrated that cortisol decreases neutrophil superoxide production, which is counteracted by coincubation with DHEAS (46). Furthermore, we have previously shown that DHEAS, but not DHEA, directly enhances neutrophil superoxide generation, a key mechanism of human bactericidal function via activation of protein kinase C-β, independent of androgen receptor signalling (50). In the present study, carried out in severely injured men younger than 50 years of age, we observed suppression of both serum DHEA and DHEAS postinjury, indicating that the loss of adrenal androgen synthesis is a trauma-related event. Importantly, we showed for the first time that this decrease in circulating adrenal androgen precursors is sustained for several months, and that DHEAS remains low even 6 months postinjury.

Alongside the decrease in adrenal androgen synthesis, we observed a near complete loss of gonadal testosterone production and pituitary LH secretion immediately after trauma. Both the gradual recovery of adrenal and gonadal androgen production paralleled the decrease in catabolism, as assessed by urinary nitrogen excretion and biceps muscle thickness. The suppression of the hypothalamus-pituitary-gonadal (HPG) axis after severe injury shown in our study is supported by the literature (51–54). Our prospective, longitudinal data demonstrate that suppression of the HPG axis is of shorter duration than that of the HPA axis. In traumatic brain injury studies, a significant proportion of patients go on to develop anterior pituitary dysfunction, including secondary hypogonadism (55). However, in our study traumatic brain injury was an exclusion criterion. While limited data from patients with burns and critical illness have suggested a central, hypothalamic-pituitary cause of trauma-related hypogonadism (56, 57), the evidence prior to our study has been limited.

Our data indicated a central cause of suppression to the gonadotrophic axis, with a decrease in both pituitary LH and gonadal testosterone. Interestingly, we observed a differential impact of the cumulative opioid dose on adrenal and gonadal androgens, respectively, with a significantly delayed recovery of DHEA and DHEAS, but a trend towards faster recovery of gonadal testosterone synthesis in patients with higher cumulative opioid doses. Previous data on opioid effects on adrenal androgen production are very scarce, but our findings with respect to gonadal testosterone biosynthesis contrasted previous studies describing suppressive opioid effects on the HPG axis (41, 42).

Our study revealed a loss of both adrenal and gonadal androgen production in young and middle-aged men after major trauma. This effect was further enhanced by long-lasting suppression of androgen-activating systemic 5α-reductase activity, as demonstrated by urinary steroid metabolite analysis. Androgens are important in wound healing, erythrocytosis, bone density, and muscle mass (58). The catabolic state that occurs following trauma thus presents a significant challenge. The use of androgens to ameliorate catabolism has some precedent, as evidenced by the use of the synthetic androgen, oxandrolone, that has some proven benefit in treating burn injuries (9). A meta-analysis of 15 randomised controlled trials of 806 burn patients by Li et al, showed significant benefits (P < 0.05) for using oxandrolone, including less net weight loss, lean body mass loss, nitrogen loss, donor-site healing time, and length of stay in the catabolic and rehabilitative phases (59). The use of oxandrolone in major trauma was investigated in 2 intensive care studies but no benefit was demonstrated (60, 61).

The strengths of our study include its prospective nature, narrow age range of the patients, single gender, single site for recruitment and analysis, and detailed follow-up over 6 months as well as the measurement of circulating (and in a smaller cohort also excreted) steroid hormones by state-of-the-art mass spectrometry assays. Analyzing a young to middle-aged patient cohort has also reduced the confounding effects of age-related comorbidities. Another strength is the unique opportunity our study offered for analysis of the opioid effects on endocrine recovery, facilitated by detailed prospective, longitudinal phenotyping with dedicated software.

Our study was limited by the diverse nature of major trauma patients in relation to injury pattern and the involvement of military casualties. The timing and number of observations during our study was pragmatic and some statistical comparisons were made using modeled
data. While we measured total cortisol and cortisone by tandem mass spectrometry, we did not measure free cortisol or cortisol-binding globulin. We were only able to measure urinary steroid excretion in a subcohort of patients, as accurate and repeated collection of 24-hour urine proved very challenging under ICU conditions. The estimation of nitrogen excretion was pragmatic due to the diverse nature of the patients and we were not able to record nitrogen intake. Ultrasound estimation of muscle thickness was performed at 4 different body sites, but many individuals had limbs missing or extensive wounds that prevented measurements. While imperfect, the longitudinal nature of these measurements allowed us to model these changes over time.

In conclusion, in this most detailed and first prospective study of the steroid response to major trauma, we followed the patients from severe injury to 6 months of recovery, revealing pronounced and sustained decreases in adrenal and gonadal androgen biosynthesis. Recovery of androgen production in the severely injured patients was mirrored by a switch from catabolism to anabolism as reflected by recovery of muscle mass and a decrease in nitrogen loss. Adrenal and gonadal androgens correlated with risk of sepsis. It is tempting to suggest that an anabolic intervention with androgens or androgen precursors could have a beneficial effect on health outcomes during recovery from major trauma. However, this will need to be investigated by future intervention studies.

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