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Dehydroepiandrosterone: a potential therapeutic agent in the treatment and rehabilitation of the traumatically injured patient

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Abstract

Severe injuries are the major cause of death in those aged under 40, mainly due to road traffic collisions. Endocrine, metabolic and immune pathways respond to limit the tissue damage sustained and initiate wound healing, repair and regeneration mechanisms. However, depending on age and sex, the response to injury and patient prognosis differ significantly. Glucocorticoids are catabolic and immunosuppressive and are produced as part of the stress response to injury leading to an intra-adrenal shift in steroid biosynthesis at the expense of the anabolic and immune enhancing steroid hormone dehydroepiandrosterone (DHEA) and its sulphated metabolite dehydroepiandrosterone sulphate (DHEAS). The balance of these steroids after injury appears to influence outcomes in injured humans, with high cortisol: DHEAS ratio associated with increased morbidity and mortality. Animal models of trauma, sepsis, wound healing, neuroprotection and burns have all shown a reduction in pro-inflammatory cytokines, improved survival and increased resistance to pathological challenges with DHEA supplementation. Human supplementation studies, which have focused on post-menopausal females, older adults, or adrenal insufficiency have shown that restoring the cortisol: DHEAS ratio improves wound healing, mood, bone remodelling and psychological well-being. Currently, there are no DHEA or DHEAS supplementation studies in trauma patients, but we review here the evidence for this potential therapeutic agent in the treatment and rehabilitation of the severely injured patient.

Keywords: Dehydroepiandrosterone, Dehydroepiandrosterone sulphate, Traumatic injury, Intensive care, Immune, Rehabilitation

Background

Before the modern era of resuscitative medicine and surgery, and the reorganisation of emergency hospital care into major trauma centres, the likelihood of survival following a traumatic injury was down to the individual's physiological response to injury. Survival is achieved via a complex set of metabolic, endocrine and immunological pathways [1–3] that mobilise fuel sources and minimise blood loss, so that our vital organs may continue to be perfused and function. There is growing interest in this physiological response to major trauma and how to manipulate recovery to improve patient outcomes further. That the response may be malleable and include modulation by sex steroid hormones is driven by clinical observations of lower mortality rates in females [4] and lower incidence of pneumonia post-injury compared to males [5]. Additionally, those trauma victims aged over 75 years have an increased morbidity and mortality rate [6]. The differences in sex steroid hormones and their precursors between genders and across the lifespan may thus influence outcomes in the trauma patient population [7].

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Review

The endocrine, immune and metabolic response to trauma

As previously reviewed [1, 3], the metabolic and endocrine response to trauma is mediated through the hypothalamus. Via baro-, volu- and pain receptors, the hypothalamus receives multiple signals as a result of the injury, which initiates the acute phase response and activation of the pituitary, adrenal and sympathetic nervous system pathways, which induces the characteristic 'fight or flight' response. Central to this response is cortisol (Fig. 1).

Cortisol is vital in the immediate response to trauma as it increases blood glucose via protein catabolism, promoting hepatic gluconeogenesis and allowing for an increase in gluconeogenic precursors from triglyceride breakdown. Cortisol also acts upon cells of the immune system, including macrophages [8] and neutrophils, preventing their excessive accumulation in damaged tissues and areas of inflammation but also potentially limiting the anti-microbial effects by inhibiting their function [9]. In addition to inhibition of cytokine production, cortisol decreases the production of pro-inflammatory leukotrienes and prostaglandins [10].

The hypothalamic–pituitary axis should, in theory, receive negative feedback from cortisol to prevent further release of corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) [1, 3]. A second adrenal steroid hormone affected by trauma is dehydroepiandrosterone (DHEA), an androgen precursor, which is mostly present in the circulation in its sulphated form, dehydroepiandrosterone sulphate (DHEAS). After injury, serum DHEAS levels fall, and the synthesis of cortisol overtakes that of DHEAS [11], which is plausibly due to inhibition of DHEA sulphation, which is down regulated in acute inflammation and sepsis [12].

Initiated via blood loss and tissue damage, damage-associated molecular patterns (DAMPs), such as high-mobility group box (HMGB)-1 [13], are secreted from activated neutrophils [14] and necrotic cells [15]. Necrotic cells evoke a strong reaction due to the release of mitochondrial DNA and cellular constituents such as formylated peptides [16, 17]. DAMPs can directly activate neutrophils and monocytes via specific DAMP receptors [14], with activation of both C3a and C5a complement [18] synergistically causing the production and subsequent release of interleukins thereby generating the systemic inflammatory response syndrome (SIRS) [2].

The SIRS response is accompanied by a compensatory anti-inflammatory response syndrome (CARS) [19], to restore homeostasis. If the resolution of inflammation is not achieved via anti-inflammatory cytokines, CARS may progress to the persistent inflammation, immunosuppression and catabolism syndrome (PICS) [20, 21]. Compounding the problems that have arisen from the initial injury, the PICS clinical picture may involve: reduced oxygen and nutrient delivery via macro and microcirculatory impairment [20]; acquired weakness in the intensive care unit (ICU) [22] and a subsequent dependence on mechanical ventilation; muscle atrophy,

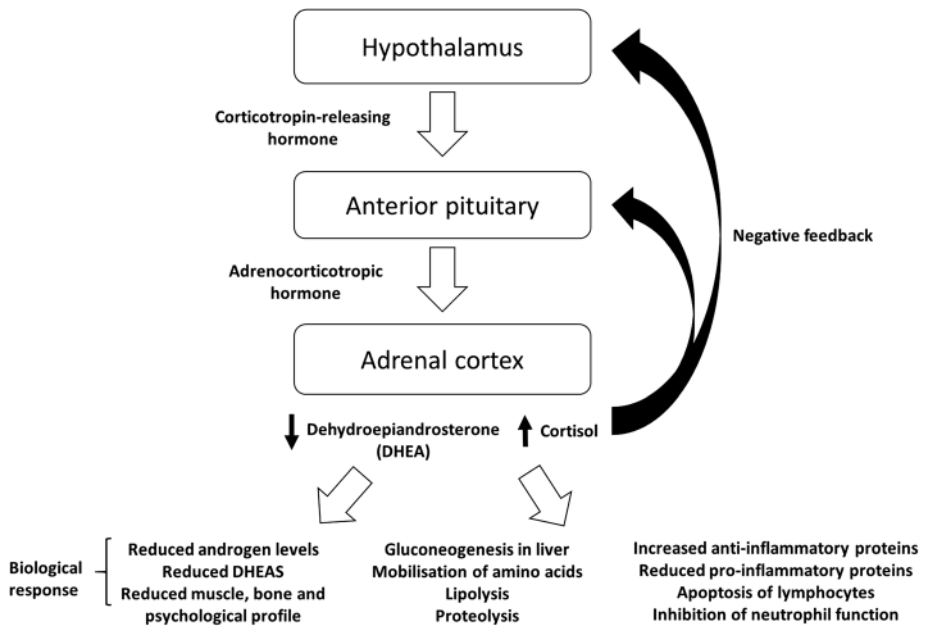

Fig. 1 The hypothalamic–pituitary–adrenal (HPA) axis and the biological responses that occur as a result of traumatic injury. The resulting increase in circulating levels of cortisol and a reduction in dehydroepiandrosterone (DHEA) has been shown to affect several biological responses, such as the inhibition of neutrophil function

which is related to increased multi-organ failure [23]; and increased sepsis [24].

Therefore, a clinically driven research solution to promote a shorter period in catabolism, more rapid return to anabolism and the recovery of immune function is required if we are to improve patient outcomes following significant injury.

DHEA/DHEAS and the response to trauma

Differences between the sexes in response to injury have been observed. Being male and a victim of trauma is associated with increased mortality, length of hospital stay and secondary complications such as infections and multiple organ failure. This suggests that the female sex steroid hormones may have a protective effect in trauma [7, 25]. The apparent female advantage [26] and differences in survival with age [27] have led to the consideration of the role of the sex steroid precursor hormone DHEA, whose levels decline with age and differ between the sexes.

DHEA is predominantly synthesised in the zona reticularis of the adrenal cortex [28] in response to stimulation by ACTH. Both DHEA and DHEAS are secreted from the adrenal cortex, with peak concentrations of 10 μM (DHEAS) and 10 nM (DHEA). In humans, serum levels of both DHEA and DHEAS change significantly across the lifespan [29]. Large amounts are produced during fetal development and after an initial rapid decline immediately after birth [30] synthesis resumes when adrenarche occurs between 6 and 8 years [31]. DHEA and DHEAS levels continue to rise throughout puberty and peak during the second decade of life with absolute levels of circulating DHEAS lower in females than males throughout life [32]. By the third decade of life, DHEA and DHEAS levels decline [33], being as little as 10–20% of peak by the eighth decade [34], a phenomenon termed the adrenopause.

DHEA is sulfonated by the sulfotransferase family 2A member 1 (SULT2A1) to DHEAS [35] in the adrenal cortex and during first-pass metabolism in the liver and, as such, would have implications upon oral DHEA supplementation. The levels of circulating DHEAS are several folds higher than DHEA [36], acting as a reserve to be readily converted by steroid sulfatase (STS) to DHEA in the endoplasmic reticulum [37, 38]. Only 5% of DHEA in males with normal testicular function is converted to testosterone [39]. However, in premenopausal females, 40–75% of the circulating testosterone comes from DHEAS. This is in stark contrast to the 90% of oestrogens that are derived from DHEAS in the postmenopausal female [39]. Some of the known biological functions of DHEA are shown in Fig. 2.

DHEA has been shown to modulate the action of glucocorticoids, such as cortisol [40]. We have reviewed the numerous immune effects of DHEA and DHEAS previously [41] and have shown that DHEAS but not DHEA enhances neutrophil superoxide generation via protein kinase C (PKC) mediated pathway, thereby augmenting an essential immune response to infection [42]. We and others have also suggested an influence of DHEA/DHEAS on anti-viral innate immune function. In Addison's disease, in which autoantibodies target the adrenal cortex, patients are supplemented with sex steroids and glucocorticoids but not DHEA/DHEAS. These patients have reduced natural killer (NK) cell cytotoxic function [43] and increased susceptibility to respiratory infections [44]. These patients also show a reduced innate anti-viral response in peripheral blood mononuclear cells, specifically reduced chemokine (C-X-C motif) ligand (CXCL)9 and CXCL10 production in response to stimulation with interferon [45]. However, supplementation with DHEA did not improve NK cell function in these patients [43].

Cortisol levels are preserved with age and, as mentioned previously, are elevated after severe injury, as well as sepsis [24]. In addition to being potent suppressors of the immune system, glucocorticoids promote an intra-adrenal shift in steroid biosynthesis, being produced at the expense of DHEAS [46]. This increases the cortisol to DHEAS ratio which is associated with a range of poor outcomes in trauma victims [47–51], with further exacerbation of this ratio in those with adrenopause, associated with suppressed neutrophil function and increased risk of infections [9].

Our group has shown in a 6-month observational study of major trauma patients that DHEAS levels were reduced within days of injury to almost undetectable levels. DHEAS remained low throughout the follow-up period, despite DHEA returning to normal by 3 months. Resolution of the DHEA: cortisol ratio to that of healthy controls provides an insight into potential clinical benefits, namely, a decrease in nitrogen excretion and increase in biceps brachii muscle thickness, suggesting a reversal of catabolism with the normalisation of DHEA levels [52, 53]. The DHEAS: cortisol ratio is proposed to represent a balance between the catabolic effects of cortisol and the regenerative effects of DHEAS [54, 55] and its modulation may benefit the trauma patient. Unlike DHEAS, DHEA is readily available in various formulations. As a result, the vast majority of clinical studies have employed DHEA supplementation as a route to influencing this ratio and our review, therefore, focusses on this intervention.

DHEA and DHEAS deficiency after trauma and critical illness

Twenty-two studies investigating the level of DHEA and DHEAS after critical illness have been identified by our

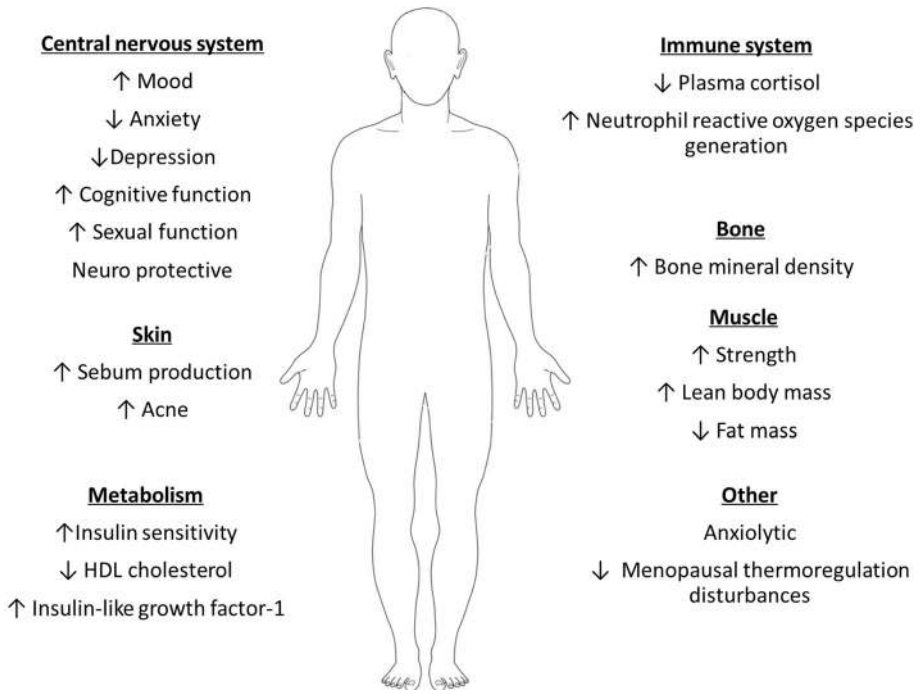

Fig. 2 The physiological effects of dehydroepiandrosterone/dehydroepiandrosterone sulphate (DHEA/DHEAS) in humans. Restoration to normal DHEA and DHEAS levels are associated with a range of positive biological functions such as, increased (↑) bone mineral density and decreased (↓) fat mass, across a range of body systems that include the bone and central nervous system (CNS), high density lipoprotein (HDL)

group [9, 11, 12, 56–74]. Only two studies have measured DHEA [72, 74] via the gold standard method of liquid-chromatography mass-spectroscopy (LC-MS) [75] in traumatically injured patient. Although Brorsson et al. [72] demonstrated a significant decrease in both DHEA and DHEAS levels within the study duration of 96 h, these short-term follow-up studies with often mixed clinical populations, make direct comparisons to the young and non-septic trauma populations unclear. Foster et al. study in 102 severely injured patients, 41 of whom were young male soldiers, identified that in addition to low DHEA and DHEAS levels for up to 6 months post-injury, the downstream suppression of androgens highlights an opportunity to intervene in adrenal androgen synthesis in the medium to longer term recovery after both battlefield and civilian trauma [53]. Despite its potential, interventional studies have yet to be designed to address both DHEAS and DHEA's ratio with cortisol in traumatically injured patients.

The benefits of DHEA and DHEAS in recovery after trauma

To our knowledge, no human studies have utilised DHEA supplementation in trauma patients at any stage of their recovery, despite being proposed [34]. Similarly, DHEAS has yet to be used as an intervention in any human trauma studies. It may be that DHEAS supplementation would be more beneficial than DHEA in potentiating the immune function, such as enhancing reactive oxygen species (ROS) production by neutrophils via activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [76]. However, what we do know is that supplementation of DHEA in healthy subjects, via oral administration, will result in first-pass metabolism and thus a conversion of DHEA to DHEAS, resulting in either immune or downstream androgen or oestrogenic benefits.

Animal models have demonstrated numerous benefits from DHEA supplementation such as improved hyperglycaemia [77], decreased mortality after trauma-induced haemorrhage [78], neurogenesis [79] and wound reperfusion [80], all of which pose a considerable burden to the recovery from injury. It is important to note that rodent adrenal DHEA production is modest [81]. Rodents possess the necessary mechanisms to convert exogenous DHEA to sex steroids [82], but caution is required in extrapolating rodent data to humans.

Inflammation and immune effects

A retrospective analysis of the trauma register from 2002 to 2005, reported bilateral femoral shaft fractures, which are often accompanied with abdominal injuries and blood loss, as being an independent risk factor for pulmonary failure [83]. A mouse model was used by

Lichte and colleagues to confer if subcutaneous DHEA administration (25 mg/kg/day) would control the systemic inflammation seen in the treatment of these injuries. Replicating the musculoskeletal damage that is observed in a bilateral femoral fracture, DHEA supplemented mice benefited from a reduction in serum tumour necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, IL-10, monocyte chemoattractant protein (MCP)-1. However, DHEA did not improve markers of pulmonary inflammation [84].

Animal and human studies indicate that steroid hormones influence cellular immunity. The reversal of trauma-induced suppression of splenocyte proliferation, macrophage TNF-α, IL-1 and IL-6 production [78, 85] and IL-2, IL-3 and interferon (IFN)-γ secretion from splenic T cells [85, 86], improved mortality rates [78] and prevention of increased serum corticosterone [86] have all been observed following the administration of a single subcutaneous injection of DHEA in rodent models of traumatic haemorrhage. Additionally, Oberbeck et al. demonstrated that DHEA supplementation normalised splenocyte apoptosis and lymphocyte migration in haemorrhagic shock [87]. In mice models of sepsis, a frequent complication in the recovering trauma patient, the administration of DHEA has been shown to improve survival [87]. Mouse models of thermal injury have demonstrated increased resistance to pathogenic challenges when compared to controls [88] and reduced inflammation and tissue necrosis [89] when subcutaneous DHEA was administered. Conversely, other forms of steroids, including DHEAS, exhibited no protective effects [89].

There are very few studies on the effects of DHEA or DHEAS on human immune cells. DHEAS has been shown to directly stimulate the action of NADPH oxidase and reactive oxygen species production and thus improve neutrophil function [42]. This effect may be unique to neutrophils as these immune cells are the only leukocytes that express the organic anion transporting polypeptide (OATP-D) required for DHEAS uptake. The very low levels of DHEAS seen after trauma may thus be a contributor to reduced neutrophil function in trauma patients [90]. In contrast, in the hyperglycaemic environment that is often present after trauma and infection, DHEA, a glucose-6-phosphate dehydrogenase inhibitor, has been shown to reduce neutrophil superoxide production in a dose-dependent manner [91].

Recently, Corsini et al. have identified DHEA conversion to androgens and subsequent binding to androgen receptors, as a necessary step in the DHEA-induced monocyte activation and its potential use for immune modulation [92]. DHEA may also prevent monocyte adhesion in endothelial cells, appearing to act via its oestradiol and dihydrotestosterone metabolites [93]. This conversion of DHEA to downstream metabolites may occur within macrophages, which may also be important for local immunomodulation, although the conversion does depend upon the maturation of the monocyte to a macrophage in tissues [94].

Wound healing

Trauma results in physical injury which may be acute (a result of the initial trauma) or chronic (due to impaired wound healing). Wound healing begins immediately after the injury and involves a series of overlapping phases with the sequential recruitment of immune cells, fibroblasts, stem cells and endothelial cells to mediate tissue repair and extracellular matrix deposition [95, 96].

Advances in surgical techniques have led to the rise in the use of tissue flaps to improve the outward appearance and functionality that has been lost. Rats pre-treated with DHEA had markedly improved muscle flap microcirculation and haemodynamics and were protected against ischaemia and reperfusion injury [80]. A similar study by Ayhan and colleagues supplemented rats with intravenous DHEA and showed a reduction in activation of leukocytes, improved red blood cell velocity and capillary perfusion in the muscle flap microcirculation, with the protective effect most likely a result of delayed expression of Mac-1 integrin, L-selectin and CD44 molecules on leukocytes [97]. Topical administration of DHEA has also acted as a mediator of tissue repair to ultra violet (UV) light damaged skin [98].

How DHEA exerts its effects on wound healing are not precisely known. Excessive inflammation is a causative factor in delayed wound healing, and DHEA supplementation inhibits nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) DNA binding activity, resulting in the dampening of gene transcription of IL-6 and TNF-α [99]. Alternatively, it may be DHEA conversion to both androgens and oestrogens that is involved, as sex hormones have also been shown to be anti-inflammatory [100, 101]. In a mouse model of age-related delayed wound healing, Mills et al. observed that topical administration of DHEA accelerated wound healing, dampened the inflammatory response via mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3 (PI3) kinase pathways. The authors suggested this beneficial response was due to DHEA conversion to oestrogen [102].

Interestingly, animal models of wound healing have shown that DHEA has no observable effects in the young. This is possibly due to circulating oestrogens being sufficient in the young, or supra-physiologically high levels of oestrogen via DHEA conversion exerting no effect upon wound healing [102]. Although this suggests that topical DHEA may benefit the older trauma patient, there is currently insufficient data to suggest

routine administration for wound healing, across all trauma demographics.

Psychological and neurological effects

Traumatic brain injury (TBI) is a major cause of mortality and morbidity, with 1.4 million patients per year attending hospital in England and Wales [103]. DHEA and DHEAS may be synthesised by the brain independently with levels higher in the central nervous system (CNS) when compared with blood [104, 105]. In rats, DHEA supplementation (40 mg/kg for 5 days subcutaneously) has been shown to promote neurogenesis in the hippocampus and survival of newly formed neurons [79]. Additionally, supplementation of a DHEA analogue has been shown to improve cognitive and motor skills via a beam walk test in TBI rats, with authors hypothesising the action via retardation of glial scar formation and neurite regrowth helping to restore reflexes and memory [106]. Hoffman and colleagues observed similar results, albeit that the DHEA administration was delayed until 7 days post-injury, with improvements in a battery of behavioural tests [107]. This benefit of DHEA directly may be via neural stem cells, increased nerve growth factor (NGF) and brain-derived neurotrophic factor, potentially conferring neurogenic, neuronal survive advantages [108, 109]. Again, no studies to date have investigated the use of DHEA supplementation in a human neurotrauma cohort, with this relatively cheap supplement, potentially providing a safe medium to long-term aid to recovery and possibly pain perception [110] in these patients.

The psychological aspect of trauma is often overlooked in recovery; with an incidence of post-traumatic stress disorder (PTSD) approximately 10% in those who have been subjected to trauma [111] and depressive symptoms in 42% of patients, issues may occur any time from 6 weeks up until 20 years post-injury [112, 113]. The DHEAS: cortisol ratio predicted stress resilience in male military personnel; lower symptoms of PTSD and depression and finally demonstrating improving symptoms over time [114]. A raised cortisol: DHEAS ratio in old hip fracture patients was associated with the development of depression after injury [49], thereby detrimentally impacting the individual during a period of immune and psychological vulnerability. A 15-year follow-up in a population of Vietnam veterans, both age-adjusted and fully adjusted analysis, showed that both cortisol and the cortisol: DHEAS ratio were positively associated with hypertension [48]. As a result, both studies suggest the need to maintain an adequate DHEAS: cortisol ratio for the prevention of long-term ill health after stressful events.

DHEA levels are also inversely correlated with depressive symptoms in adults under 64 years [115], with higher serum DHEAS levels in older adults shown to be protective against the onset of depression [116]. Unfortunately, in the healthy older population, DHEA supplementation has not proven beneficial for well-being and depressive symptoms [117]. DHEA supplementation in those with moderate depression [118] and psychiatric disorders [119–121] and adrenal insufficient women [122] has shown potential for mental health. In older men, a relatively low dose of 25 mg of DHEA per day showed improvements in joint pain, hormonal profile and clinical status [123]. A 6-month DHEA supplementation of males and females with profound androgen deficiency noted minor to modest improvement in psychological well-being [124]. However, it is when DHEA is converted to DHEAS that a greater impact upon the gamma-aminobutyric acid (GABA) [125] and the N-methyl-D-aspartate (NMDA) [126] receptors may result in a psychological benefit.

Body composition

Several studies have suggested a positive effect of DHEA on bone biology. Wang and colleagues treated ovariectomised mice with DHEA and observed a significantly increased bone cancellous compared with that of control, suggesting that DHEA can improve bone tissue morphometry of this postmenopausal model [127]. In a further sub-study with the calvariae of neonatal mice, the authors proposed that DHEA increases the anabolic metabolism-related organelle content in osteoblasts, improving mechanical strength [127]. A recent study investigating the effect of a *Brucella abortus* infection on mouse osteoblast function showed that DHEA treatment reversed the effect of the infection upon osteoblasts by increasing their proliferation, inhibiting apoptosis and restoring differentiation and function [128].

In postmenopausal women, DHEA given orally increased bone mineral density in both the lumbar spine and femoral neck [129], which may be attributable to the conversion of DHEA to both oestrogens and active androgens in bone [130]. DHEA appears to promote the proliferation and inhibition of osteoblasts via the MAPK signalling pathway independent of an androgen or oestrogen receptor, thus suggesting the supplementation may directly exert its effect via a specific DHEA receptor [131]. Additionally, the osteoanabolic action of DHEA may act upon the adrenally insufficient patient by increasing levels of osteocalcin and bone mineral density (BMD) [132–134]. A 6-month 50 mg DHEA supplementation in older males with low DHEAS levels improved total body BMD [135]. Improved BMD was also observed in osteoporotic patients when administered 100 mg per day of DHEAS over the same period [136]. In 225 women, aged 55–85, who were supplemented with 50 mg per day for 1 year, a positive effect upon the lumbar spine BMD

was observed [137]. Jankowski and colleagues also investigated the effect of DHEA supplementation upon those with low levels of DHEAS. Their study of 70 males and 70 females demonstrated significant improvements when compared to placebo, for an increase in hip BMD in both sexes and spine BMD in females [138]. As traumatic injuries and hip fractures are comprised of characteristic long bone and soft tissue injury, the potential effect of DHEA as a means of improving a patient's bone profile in recovery may be advantageous.

The loss of muscle mass and function with age, sarcopenia, has also been targeted by DHEA. However, the effect upon males has been variable, from a minimal effect on muscle mass [139] to reduced body fat and increasing muscle strength after 1 year of DHEA supplementation [140]. A 6.1% reduction in fat mass in healthy 50–65-year-old males, with significant improvement in measures of muscle strength of the knee (15%) and lumbar strength (13.9%), has been reported with 6 months of DHEA [141]. DHEA was also able to reduce both visceral and abdominal fat while improving insulin sensitivity [141]. These beneficial effects upon insulin sensitivity may be mediated by increased oestrogen and androgen levels, but also independently, by an increase in Insulin-like growth factor (IGF)-1 [142], an important anabolic hormone. Studies in adrenal insufficiency, which may mimic the low levels of DHEA and DHEAS seen after trauma, did not reveal any significant effect of DHEA replacement on body composition, or bone parameters [132–134, 143, 144]. The rapid and prolonged loss of muscle mass, as well as low levels of DHEA, increase the risk sepsis in trauma populations [52, 53]. Therefore, DHEA supplementation may improve both the size and strength of the rehabilitating patient as well as helping to support organ function during acute illness especially as a result of ICU-acquired weakness.

Benefits of DHEA over up and downstream sex hormone supplementation

DHEA is the precursor for the androgenic and oestrogenic hormones. It is unlikely that supplementation of 17α-hydroxypregnenolone or pregnenolone (upstream steroid hormones) would be of benefit as both may be converted to cortisol during the stress response. After the initial acute phase of injury, when cortisol is essential, prolonged hypercortisolaemia in the weeks after injury may initiate immunosuppression by exacerbating the trauma-induced increase in the circulating concentration of this glucocorticoid [145].

Downstream androgens, such as testosterone, have been considered. Driven by the need to overcome liver toxicity of exogenous testosterone supplementation, the analogue oxandrolone has been used in both adults [146] and children [147]. Although its use has been unproven in the first month after trauma in a mixed population [148], it is in burn injury, where it has been seen to act positively to mitigate the hypermetabolism and catabolism observed in those who have a total burns surface area of > 20%, without side effects [149]. Oxandrolone still requires well-designed optimal dose-finding studies to be undertaken in the heterogeneous trauma population so that the efficacy and safety of this drug may be put through the rigour of a larger multi-centre randomised controlled trial [150], over an effective duration, in order to overcome the hypermetabolic and catabolic state observed after injury across a range of demographics [52, 53].

In summary, DHEA has potential advantages over supplementation with downstream hormones. As the precursor for the androgenic and oestrogenic hormones, it can benefit male and female patients, and unlike oxandrolone, it may be converted to DHEAS which we have previously shown to enhance neutrophil function and thus potentially offer protection against infection [9, 42].

Practicalities: dosing, delivery and safety of DHEA supplementation studies

Consideration and challenges in a trauma cohort

Studies investigating the dosing and delivery routes of administration of DHEA supplementation trauma patients are fraught with difficulties. As patients will be critically ill, there is a high likelihood that they will be subjected to polypharmacy. This may adversely affect the true profiling of DHEA. Nevertheless, there are some key factors to consider for any DHEA supplementation study.

Due to DHEA metabolism in the liver, any patients with pre-existing or chronic liver failure should not be recruited; known thromboembolic events in the last 12 months and any pre-disposition to thrombosis are also contraindicated, as DHEA's androgenic potential may result in altered coagulation [151]. As patients clinical therapy may involve the administration of drugs and blood products to counteract any blood loss or long-term admission, daily monitoring of changes to document adverse events are necessary. Patients taking hormone replacement therapy, antipsychotic medication and with known hypersensitivity to DHEA [152], should be excluded. Similarly, those who have known or previous hormone-sensitive malignancies or invasive cancer, and prostatic hypertrophy due to DHEA supplementation increasing downstream metabolites in both males [153] and females [154] may need to be excluded. Although women with poor oocyte production have been shown to benefit positively from DHEA supplementation of 50 mg/day [155], the recruitment of pregnant trauma patients would be inadvisable due to the lack of available data.

Concurrent DHEA and testosterone therapy have not been tested, but available data suggest the avoidance of such an approach [152], due to oral DHEA increasing endogenous testosterone [156]. Therefore, intake of any drugs influencing the metabolism of steroids in the months before injury should act as an exclusion criterion for potential patients [157]. Administration of progesterone and DHEA may also yield false-positive results when it comes to using commercially available progesterone assays [158], which may be overcome by using LC-MS [75].

Maxillo-facial injuries or a non-functioning gut may prohibit sublingual or oral administration and compliance to the study protocol; therefore, an adaptable study design is needed to generate pilot data. By monitoring gastric residual volumes (GRV), a surrogate marker of gastrointestinal motility [159], and seeking expert statistical advice on overcoming potential trial pitfalls, identification of an appropriate dose and route of DHEA may be identified for use in a randomised controlled trial.

Current DHEA therapeutic indications, investigated doses and method of administration

Researchers have attempted to circumvent first-pass metabolism by providing DHEA supplementation via different formulations and routes. Transvaginal [160], transdermal [161], subcutaneous pellets [162] and buccal/sublingual [163, 164] routes have all been investigated and shown to increase the DHEA: DHEAS ratio. Oral and buccal/sublingual delivery provide the most broadly acceptable and practical route for self-medicating. However, for any future clinical trials, the method of delivery must be one that is not only efficacious but feasible given the injuries sustained.

A DHEA buccal dose of 50 mg can increase free testosterone, total testosterone, androstenedione and DHEAS levels, with 5 mg shown to double DHEAS within 5–10 h, prior to returning to the pre-treatment levels within 24 h [163]. However, in the most investigated cohort, peri-menopausal females, 90% of studied doses have been at $\leq$ 50 mg/day given orally [165]. Previous studies have shown that supplementation with 50 mg DHEA orally once daily in the older population restores serum DHEA and DHEAS levels to that of men and women in the third decade of life [166, 167]. As expression and activity of steroid metabolising enzymes in peripheral target tissues, which may be influenced by inflammatory cytokines [38], we cannot assume that downstream conversion of DHEA in patients with acute trauma and associated inflammatory response will be identical to that in healthy volunteers. Thus, the pharmacological profile of DHEA supplementation via different routes, at different doses in recovering trauma patients requires investigation via an innovative study design.

Possible side effects of DHEA supplementation

Cochrane reviews of DHEA supplementation in peri- and post-menopausal females [165], systemic lupus erythematosus [168], assisted reproduction [169] and older

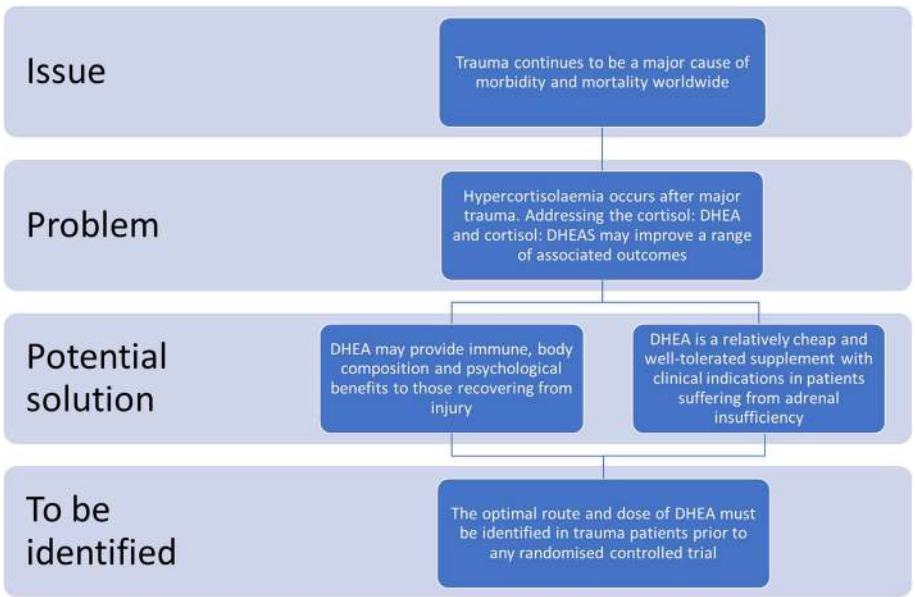

Fig. 3 Dehydroepiandrosterone/dehydroepiandrosterone sulphate (DHEA/DHEAS): a potential therapy to the burden of traumatic injury? A schematic diagram identifying if this safe, well-tolerated, early sex-steroid could be added to the future care package of those who have been injured? Well-designed studies are needed first to identify the dose and the route of administration, prior to any large multicentre, randomised controlled trial

adults [117] have attempted to assess its safety. Although DHEA has been used at different doses with no deleterious side effects, longer-term studies have reported mild cases of hirsutism and acne [170–172]. The highest daily dose reported to date, in both males and females, was 1600 mg/day for 28 days [173]. Nair and colleagues undertook the longest placebo-controlled, randomised, double-blind study in older men (75 mg/day) and women (50 mg/day) for 2 years. The authors monitored prostate volume, prostate-specific antigen, liver function, electrolyte levels and haemoglobin and did not observe any significant differences between the groups [174].

From the published literature, we could only find four publications that have utilised the sublingual and/or oral route for administration of DHEA. The studies used different daily doses of DHEA varying from 10 to 50 mg and were carried out for 2 weeks to 4 months [163, 164, 175, 176]. In only one of these four studies [164] was mild acne reported as a side effect of supplementation. The current data suggest that DHEA, certainly in short-term supplementation, should be regarded as safe without significant side effects. However, the outcomes, dose and administration route of DHEA supplementation require confirmation via feasibility and pilot studies in those with traumatic injury (Fig. 3).

Conclusions

The endocrine response to traumatic injury has been well studied. However, the role of DHEA and DHEAS in severe clinical trauma is relatively unexplored, with the majority of studies focusing upon the cortisol responses. This is despite recent data suggesting that it is the cortisol to DHEAS ratio that is the superior prognostic factor for short and long-term outcomes. Results have indicated that levels of the early sex-steroid hormones, DHEA and DHEAS, are low immediately after injury and remain below normal for over 6 weeks and longer, particularly in the older patient. Animal models and previous reviews have hypothesised that exogenous supplementation of DHEA is warranted. The immunological, anabolic, neurocognitive, wound and mood enhancing profile reported in animal models, and also some human studies, provide an opportunity to support trauma patient recovery holistically. However, there is a need for studies in the trauma population to first identify the dose, route and duration of DHEA supplementation that would restore levels to those of the healthy adult.

Abbreviations

ACTH: Adrenocorticotropic hormone; BMD: Bone mineral density; CARS: Compensatory anti-inflammatory response syndrome ; CNS: Central nervous system; CRH: Corticotropin-releasing hormone; CXCL: Chemokine (C-X-C motif) ligand; DAMPs: Damage-associated molecular patterns; DHEA: Dehydroepiandrosterone; DHEAS: Dehydroepiandrosterone sulphate; HDL: High density lipoprotein; GABA: Gamma-aminobutyric acid; HMGB: High-mobility group box; ICU: Intensive care unit; IFN: Interferon; IGF: Insulin-like growth factor; IL: Interleukin; LC-MS: Liquid-chromatography mass-spectroscopy; MAPK: Mitogen-activated protein kinase; MCP: Monocyte chemoattractant protein; NADPH: Nicotinamide adenine dinucleotide phosphate; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; NGF: Nerve growth factor; NK: Natural killer; NMDA: N-methyl-D-aspartate; OATP-D: Organic anion transporting polypeptide; PI3: Phosphatidylinositol 3; PICS: Persistent inflammation, immunosuppression and catabolism syndrome; PKC: Protein kinase C; PTSD: Post-traumatic stress disorder; ROS: Reactive oxygen species; STS: Steroid sulfatase; SIRS: Systemic inflammatory response syndrome ; SULT2A1: Sulfotransferase family 2A member 1; TBI: Traumatic brain injury; TNF: Tumour necrosis factor; UV: Ultra-violet

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Authors' contributions

CB has written the manuscript. JH, CG, MF, and JL reviewed and edited the manuscript. All authors approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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