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CLINICAL COMMENTARY

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Is there a role for dehydroepiandrosterone replacement in the intensive care population?

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Adrenal insufficiency in the intensive care population is becoming recognised as a cause of the increased morbidity and mortality seen in these patients. However, currently there is no consensus as to what constitutes 'adrenal insufficiency' in critically ill patients. Most authors agree that the condition is diagnosed by the lack of an appropriate rise in circulating cortisol after adrenal stimulation with an intravenous bolus of synthetic adrenocorticotrophic hormone (ACTH). However, there remain controversies over what dose of synthetic ACTH to use (1 or 250 μg), and what should be the cut-off point in cortisol levels that definitively diagnoses someone as being hypoadrenal.

Depending on the definitions used, incidence rates of adrenal insufficiency in subjects on intensive care vary between 10% and over 75% [1, 2]. There are several factors that are important in the development of adrenal insufficiency. These include sepsis, iatrogenic adrenal suppression due to previous glucocorticoid use, HIV, increasing age and length of stay [1].

In the early stages of critical illness there is a hypothalamically driven surge in glucocorticoid release, but if the critical illness continues, or if drugs that effect adrenal function such as etomidate are used, levels of ACTH and cortisol may change. There are however, patients who may be admitted to the ICU who have rapid suppression of their hypothalamic-pituitary-adrenal axis early in their condition. The initial surge in glucocorticoid production may be due to a shift in enzyme activity in the steroid synthesis pathway within the adrenal gland. These shifts lead to a relative reduction in mineralocorticoid levels and an increase in glucocorticoid release causing hyperreninaemic hypoaldosteronism [3, 4]. There is now a body of work to suggest that glucocorticoid replacement in intensive care reduces morbidity and mortality in this patient population [5, 6]. Another study also supported the use of low-dose mineralocorticoid replacement in this population [2]. How-ever, because this study had no control arm with glucocorticoid only, and the absorption of oral drugs in critical illness remains questionable, these results remain to be confirmed.

Apart from glucocorticoids and mineralocorticoids, the healthy adrenal gland also produces a third hormone, dehydroepiandrosterone (DHEA). DHEA (3β-hydroxy-5-androsten-17-one) and its sulphated ester (DHEAS) are secreted in vast quantities from the adrenal glands. These hormones are two of the major C_{19} steroids secreted by the zona reticularis region of the adrenals under the influence of ACTH. Although DHEA is often quoted as being an 'adrenal androgen', currently there is no evidence that DHEA binds to the androgen receptor, or that it has any intrinsic androgenic activity. DHEA is a prehormone that is converted into androgens and oestrogens within peripheral tissues [7]. DHEA levels are lowest in childhood, but after puberty levels increase to reach a peak in late teenage years. Thereafter levels decline by approximately 10% per decade, such that individual aged 80 years may have only 10–15% of levels found in their late teens [8]. It has been proposed that this age-related decline is due to a reduction in 17,20-lyase activity [9]. However, whether the rapid decline in DHEA levels during acute critical illness is due to a reduction in the activity of 17,20-lyase, a reduction in ACTH stimulation, or due to other reasons, remains unknown.

Because of the physiological decline in DHEA with time, normal ageing may be considered a DHEA defi-

cient state. This decline in DHEA levels with age may explain the increase in 'age related disorders' such as diabetes mellitus, cardiovascular disease and 'sarcopenia' – the decline in skeletal muscle quantity and quality. Large-scale randomised studies are currently in progress in the well elderly looking at DHEA replacement to determine whether restoration of levels to those seen in late teenage years has beneficial effects on ageing. In chronically hypoadrenal individuals the current standard of care is glucocorticoid and mineralocorticoid replacement therapy, usually as hydrocortisone or prednisolone and fludrocortisone. DHEA is not usually replaced. The question of the usefulness of DHEA in the well elderly and chronically hypoadrenal subjects has been reviewed elsewhere [10]. However, there are in vitro and animal data as well as circumstantial human evidence to suggest that DHEA replacement in the acutely ill would be of benefit.

There are conflicting data describing the changes in circulating levels of ACTH and adrenally derived hormones in critical illness. There has been some work to show that ACTH levels either decline [11] or remain high [12] as critical illness continues. Most studies agree that cortisol levels rise in early critical illness, although the degree of rise may be lower in non-survivors. This initial rise is presumably to counteract the inflammatory cytokine response associated with sepsis and trauma [13]. A recent study has shown that cortisol levels did drop with prolonged critical illness, and that there was a non-significant trend for the nadir in cortisol levels to be lower in non-survivors than in survivors [14]. The authors postulate that the higher levels seen in the survivors are due to recovery from the initial insult. However, this remains speculative.

DHEA levels drop substantially in the acute phase of critical illness and remain low in prolonged illness [15]. Lower levels of DHEA and DHEAS have been described in non-survivors of sepsis [14, 15]. However, the recent study by Marx et al. [14] showed that DHEA levels in survivors were initially higher during early sepsis but later declined to levels below those of non-survivors. DHEAS levels in survivors were approximately 15% lower than age-matched normal values at the onset of critical illness and declined to 67% lower by the time the acute episode had ended. This is in contrast to non-survivors, where DHEAS levels were almost 80% lower than aged matched controls at the onset of critical illness but did not change during the course of the illness. The reasons for these discrepancies between DHEA and DHEAS remains unknown, but as interconversion between the hormones is mediated by the actions of 3β-hydroxysteroid sulphotransferase and sulphohydrolayse, it may be that critical illness alters the activity of these enzymes to enable circulating cortisol levels to remain as high as possible for as long as possible. This shift in enzyme activity would lead to an inability to maintain the circulating DHEA pool.

The effects of DHEA on the immune system in humans have yet to be fully worked out, but there is emerging evidence that it is of benefit and acts as an immunostimulant. In vitro, DHEA has been shown to activate the monocyte-macrophage system in lipopolysaccharide-induced models of sepsis [16]. In animal models DHEA has been found to antagonise the immunodepressant effect of corticosteroids on lymphocytes [17]. DHEA has also been shown to have a direct immunostimulatory effect on murine T cells [18]. This represents one of the few DHEA receptors characterised so far. In animal models of surgically induced sepsis DHEA preserved immune function and decreased mortality [19]. Early results have also suggested that DHEA has some antiviral activity, as well as activity against parasites. These results may in part be due to DHEA being able to maintain interferon γ levels.

Studies in humans have shown that DHEA stimulated $CD4^+$ T helper cells and natural killer cell activity by directly enhancing Th1 $CD4^+$ cells, thus increasing the cytokines (in particular interleukin 2) derived from this T-helper subset [20]. This occurs at the same time as DHEA decreases Th2 cell activity [20]. DHEA also has an immunomodulatory effect by antagonising the immunosuppression of high glucocorticoid levels. In healthy postmenopausal women DHEA supplementation also improved immune function [21].

Whilst it is clear that glucocorticoids are essential for the preservation of haemodynamic stability, cortisol is a catabolic hormone; thus the increase in cortisol levels seen in critical illness may be as part of the general counterregulatory response that prepares the body for a period of nutritional deprivation. Cortisol maintains glucose levels from hepatic glycogenolysis and liberates gluconeogenic precursors such as amino acids from skeletal muscle protein breakdown for use in higher priority tissues. Prolonged hypercortisolism may be partly responsible for the decline in muscle bulk and skeletal muscle quality seen in ICU patients.

Muscle wasting and weakness is common in prolonged critical illness. This sarcopenia is due to changes in skeletal muscle protein turnover such that whilst there may be increases in skeletal muscle protein breakdown, there is also impairment of protein synthesis leading to a net decline in skeletal muscle protein content. Some studies in the well elderly who have age related reduction in quality and quantity of skeletal muscle have shown that DHEA replacement has improved muscle strength and increased lean body mass [22]. The mechanism for this has yet to be determined. Whether DHEA alters skeletal muscle protein synthesis rates per se must also be determined.

Critical illness is associated with hyperglycaemia [23]. This may in part be due to the counterregulatory response of cortisol, glucagon and growth hormone. Tight glycaemic control has been shown to decrease morbidity

and mortality on the intensive care unit [24]. However, it is not known whether the improvement in outcomes in these studies was due to the lowering of blood glucose or the increase in circulating insulin levels. It has previously been shown that survivors from intensive care are have higher serum levels of insulin that non-survivors [25]. Insulin is an anticatabolic hormone at physiological levels, i.e. it prevents skeletal muscle protein breakdown which leads to maintenance of muscle strength and improved wound healing. DHEA has been shown to improve insulin sensitivity in animal models [26]. This effect of DHEA may be because it increases phosphatidylinositol 3-kinase and protein kinase C activities, or it may mimic atypical protein kinase C activity, thus preventing glucocorticoid induced insulin resistance [27]. Whilst improvement in insulin sensitivity with DHEA replacement has yet to be convincingly demonstrated in human studies, there is epidemiological data to show that low DHEA levels have been associated with hyperglycaemia and insulin resistance [28]. It is possible therefore that DHEA administration in the critically ill will help to overcome the catabolic effects of high cortisol as well as reduce the hyperglycaemia and increased skeletal muscle protein breakdown seen as a result of the insulin resistance of critical illness.

In summary, whilst there is circumstantial evidence that DHEA replacement in adrenal suppression may be beneficial, it is clear that there is a need for randomised trials to assess the effects of this enigmatic prehormone in critical illness before routine use can be recommended.

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