A review of the role of testosterone in the care of the critically ill patient

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Testosterone is an anabolic and androgenic steroid hormone therapeutically used to produce male sex characteristics. It has also been shown to have a modulating effect on proinflammatory biomarkers. Critical illness is characterised by a proinflammatory and catabolic state and is accompanied by altered testosterone production, which may persist into the recovery phase. Testosterone may, therefore be a potential therapeutic option in critical illness. This paper reviews normal testosterone physiology, and the changes seen during critical illness and systematically reviews testosterone therapy during both the acute and chronic phases of critical illness.

Contribution of the study
This article explains the pathophysiology of testosterone during critical illness and explores the therapeutic value of testosterone in the management of critically ill patients.

Testosterone is part of a group of steroid hormones synthesised from the precursor molecule cholesterol. Steroidogenesis occurs in the gonads, adrenal cortex and the placenta. The type of steroid hormone produced depends on tissue-specific enzymes. Testosterone regulates sexual differentiation, producing male sex characteristics, spermatogenesis and fertility. Controlled by the hypothalamic-pituitary-gonadal axis, its effects are mediated through androgen and oestrogen receptors. Given the wide distribution of these receptors, testosterone has a significant biological action on several systems.

Testosterone's anabolic and androgenic effects have been shown to modulate proinflammatory biomarkers.[1] Critical illness is characterised by a proinflammatory and catabolic state and is accompanied by altered testosterone production, which may persist into the recovery phase. Testosterone may therefore be a potential therapeutic option in critical illness. This paper examined normal testosterone physiology as well as the changes seen during critical illness. We then conducted a semi-structured literature review of testosterone therapy during both the acute and chronic phases of critical illness.

Methods

For the review of testosterone production, physiology, metabolism and pathophysiology, we conducted a semi-structured literature search using the following PubMed MESH terms: 'testosterone' OR 'androgens' cross-referenced with 'biosynthesis', 'physiology', 'neurosecretory systems/physiopathology', 'therapeutics', 'inflammation', 'critical illness', 'sepsis' and 'shock'. From the search results, we selected publications deemed to be relevant to this review, focusing largely on publications within the last 5 years and those highly regarded or commonly referenced.

We then conducted a focused review of testosterone therapy strategies in critically ill patients during the acute phase of illness, as well as during the recovery phase. We used the following MESH search terms: 1) testosterone congeners; 2) therapeutics; and the combination of 3) critical illness OR sepsis OR shock OR inflammation OR systemic inflammatory response syndrome (Table 1).

For each citation, we reviewed the title and abstract to determine if it addressed the use of testosterone in critical illness. If a citation contained a possibly relevant study the article was retrieved to undergo full text evaluation. Full texts of all citations identified as being potentially relevant were then evaluated to determine eligibility. Further articles were added after manually searching the references of included studies.

All searches were conducted across the PubMed, Embase, ProQuest, Cochrane and Science Direct databases. The search was conducted on 21 July 2021 and updated on 4 July 2023.

Results

The semi-structured literature review of testosterone production, physiology, metabolism, pathophysiology and inflammatory modulation identified 76 relevant publications, the results of which are presented in a narrative synthesis below.

Testosterone synthesis and physiology

Testosterone production is controlled by the hypothalamic-pituitary-testicular axis, with a small amount produced from the adrenal cortex, placenta and brain.[2] Hypothalamic neurons contain the *Kiss*-1 gene and produce the amino acid peptide, Kisspeptin. Kisspeptin stimulates the production of gonadotropin-releasing hormone (GnRH).[3] GnRH

Table 1. Example of PubMed search

Number	Search terms	Citations
#1	((((Critical Illness) OR (sepsis)) OR (inflammation)) OR (Systemic Inflammatory Response Syndrome)) OR (shock)	1 099 625
#2	Testosterone congeners	90713
#3	#1 AND #2	1,16
#4	Therapeutics	6,89 606
#5	#3 AND #4	572

is released into the hypophyseal portal circulation and carried to the anterior pituitary where it stimulates the production and secretion of the gonadotropic hormones luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

LH and FSH are structurally similar and are produced in both men and women. In men, LH acts on the Leydig cells of the testes stimulating the production of testosterone and FSH acts on the Sertoli cells where it plays a role in spermatogenesis. In women, LH acts on the ovaries to stimulate androgen production while FSH facilitates the aromatisation of androgens to oestrogens. GnRH is released by the hypothalamus in a pulsatile fashion. GnRH immediately causes the anterior pituitary to release FSH while LH is only released after a more prolonged GnRH secretion.[3] LH binds to a G protein-coupled receptor found on the surface of Leydig cells. This luteinizing hormone receptor (LHR) activates the cyclic AMP signalling pathway and initiates testosterone production.[3]

Cholesterol, derived through dietary intake or synthesised from acetyl-CoA, is the precursor molecule of all steroid hormones. Testosterone production starts with the transport of cholesterol into the mitochondria of Leydig cells. Once inside the mitochondria, cholesterol's side chain is cleaved by the cytochrome P450 enzyme, CYP11A1, to form pregnenolone. The hydroxyl group on pregnenolone's third carbon atom is then oxidised by the 3-beta-hydroxysteroid dehydrogenase thereby forming progesterone. In the endoplasmic reticulum, progesterone is converted into androstenedione. 17-beta-hydroxysteroid dehydrogenase then converts androstenedione into testosterone.[2] In the bloodstream, testosterone can be further metabolised into dihydrotestosterone (DHT) by 5-alpha-reductase or into oestrogen through the effect of the aromatase enzyme.[2,3] Testosterone, DHT and oestrogen are all transported in the blood as either free hormones or bound to the carrier protein, sex hormone binding globulin (SHBG).

Testosterone and DHT exert their effect through the androgen receptor. A portion of the androgen receptor, the N-terminal domain, contains an area of 9 to 36 glutamine residues, which is termed the poly-Q. A longer poly-Q is associated with lower androgen receptor activity and higher serum testosterone levels.[4] When testosterone or DHT bind to the androgen receptor it modulates gene transcription in target tissues and given the wide distribution of the receptor, affects several organ systems. In this way, testosterone influences bone density, cardiovascular health, glucose metabolism, immune function and muscle and fat composition.[5] These changes occur slowly and are referred to as the 'classical' or 'genomic' effects of testosterone. Testosterone and DHT also have rapid effects that do not rely on altering gene transcription. These are referred to as the 'non-classical' or 'non-genomic' effects of testosterone.[5]

Animal studies show that the non-genomic effect of testosterone causes an increase in intracellular calcium in several different cells, including macrophages, osteoblasts, myocytes and Sertoli cells. Other non-genomic effects of testosterone are seen in its ability to activate second messenger pathways, regulate GnRH release and influence behaviour.[6] An

important effect of testosterone is its ability to cause both vasodilation and vasoconstriction. Testosterone causes vascular smooth muscle relaxation by activating voltage-gated potassium channels and inhibiting L-type calcium channels. Testosterone also modulates vascular tone by causing an increase in nitric oxide synthase and phosphodiesterase-5 activity and a decrease in the activity of asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide synthase.[7]

Negative feedback to the hypothalamus occurs in multiple ways. As testosterone levels rise, hypothalamic expression of *KiSS*-1 mRNA is suppressed, resulting in decreased GnRH production. High oestrogen levels inhibit the production of LH and Inhibin B, a hormone secreted by Sertoli cells in response to FSH, and serve as negative feedback to suppress the production of FSH.[3] Other centrally acting inhibitors of GnRH and gonadotropic hormones are leptin, prolactin and corticotropin-releasing hormone.[8]

Testosterone pathophysiology during acute illness

Numerous studies have shown that critical illness causes low serum testosterone levels in men.[9-13] The mechanism behind this phenomenon is multifactorial and differs in the acute and prolonged phases of critical illness. Causes include dysregulation of the hypothalamic-pituitary-gonadal axis, impaired Leydig cell function and increased metabolism or aromatisation of testosterone.[14,15] The onset of critical illness causes a marked drop in testosterone levels on day one,[16,17] reaching a nadir on day 3 and may take up to 2 months to return to normal levels.[17]

During the recovery phase of critical illness, the hypothalamus fails to secrete GnRH, causing reduced LH and FSH production. This hypogonadism seen in the recovery phase of critical illness is only partly curable with the administration of exogenous GnRH, which hints at the multifactorial nature of the pathology. Women however maintain normal testosterone levels during critical illness, with increases in oestradiol levels seen in post-menopausal women.[12]

Correlating the degree of testosterone suppression with the severity of the disease has shown conflicting results. Almoosa *et al.*[18] and Sahana *et al.*[19] found no correlation between admission testosterone levels and the severity of the disease. However, Foster *et al.*[17] showed that testosterone levels correlate with sequential organ failure assessment (SOFA) scores during the first 4 weeks following the onset of critical illness (autocorrelation factor of −0.79).

During the SARS-CoV-2 (COVID-19) pandemic, male patients showed a higher likelihood of developing severe disease or dying from it. Consequently, several studies examined the relationship between sex hormones and COVID-19. A study by Dhindsa *et al.*[20] on sex hormones and disease severity in men with COVID-19 showed that testosterone levels at presentation were inversely proportional to the odds of developing severe disease (p=0.02), requiring ICU admission (p=0.007) and needing ventilation (p=0.01).[20] Infante *et al.*[21] found that admission testosterone levels in male patients admitted to ICU with severe COVID-19 were significantly lower (p=0.005) and

admission oestradiol/testosterone ratios (a marker of aromatisation) were significantly higher (*p*=0.006) among non-survivors. Results showed that total testosterone levels were inversely related to the risk of in-hospital mortality (odds ratio (OR) 0.99, *p*=0.008). Cai *et al*.[22] conducted a meta-analysis of 22 studies investigating the relationship between sex hormone levels and COVID-19. Results of the meta-analysis showed that patients with COVID-19 had lower free testosterone levels (weighted mean difference (WMD) -0.05, 95% confidence interval (CI) −0.13 - 0.04), higher FSH levels (WMD 0.6, 95% CI −0.14 - 1.35), higher LH levels (WMD 0.92, 95% CI 0.12 - 1.72), lower oestradiol levels (WMD 0.88, 95% CI −2.19 - 3.95), increased progesterone levels (WMD 0.01, 95% CI −0.05 - 0.07), increased SHBG levels (WMD −8.69, 95% CI −17.2 - −0.18), an increased testosterone/LH ratio (WMD −0.95, 95% CI −1.36 - −0.55), an increased FSH/LH ratio (WMD −0.66, 95% CI −0.74 - −0.57) and an increased oestradiol/testosterone ratio (WMD 0.4, 95% CI 0.18 - 0.63).

The hypothesised role of testosterone in the pathogenesis of COVID-19 lies in its effect on the angiotensin-converting enzyme 2 (ACE2) protein and the transmembrane serine protease 2 (TMPRSS2) enzyme.[23] Testosterone increases the expression of both ACE2 and TMPRSS2, thereby facilitating the binding of the spike protein to the alveolar epithelium. Oestrogen inhibits proinflammatory cytokines, enhances cellular immunity and inhibits Nuclear Factor-κB (NF- κB) mediated cytokine production.[24] This likely explains why premenopausal women have better survival rates than men when infected with COVID-19 infection.

Hypotestosteronaemia is also associated with a longer duration of hospital stay[18,25] and increased mortality.[9,16,19] The effect of hypotestosteronaemia on the length of ICU stay and the need for mechanical ventilation has shown varying results. Two studies have shown that hypotestosteronaemia is associated with an increased length of ICU stay and that testosterone levels measured within the first 4 days of the onset of critical illness may be predictive of the length of ICU stay (*p*<0.001).[18,25] However, a prospective observational study involving 105 male patients needing mechanical ventilation for acute respiratory failure, showed no association between degree of testosterone suppression and length of ICU stay.[16] Three studies have shown an association between hypotestosteronaemia and prolonged need for mechanical ventilation.[16,18,25] However, an observational pilot study including 18 septic male patients needing mechanical ventilation, showed no difference in testosterone levels (measured at day 7 post-intubation) among those patients who had been extubated and those who needed ongoing ventilatory support (*p*=0.45).[10]

Traditional testosterone therapy

Testosterone has been traditionally used for the treatment of primary or secondary hypogonadism. Results from the Testosterone Trials[26] show that testosterone replacement therapy in elderly, hypogonadal men improved symptoms of sexual dysfunction and depression and increased bone mineral density and haemoglobin. There was no beneficial effect on measures of cognitive or physical function. The effect of testosterone on cardiac biomarkers was also assessed.[27] The group receiving testosterone therapy had a greater reduction in total cholesterol (−6.1 mg/dL, *p*<0.001), HDL cholesterol (−2 mg/dL in the treatment group, *p*<0.001) and non-HDL cholesterol (−4.2 mg/dL, *p*=0.005). There was no significant change in the ratio of total cholesterol to HDL (*p*=0.81) or triglycerides (*p*=0.47). Markers of insulin resistance, body composition, inflammation, fibrinolysis and myocardial damage were not significantly affected.

Diabetes mellitus is associated with hypotestosteronaemia, possibly due to the increased production of proinflammatory cytokines which suppress the production of GnRH.[28] The use of insulin therapy to improve glycaemic control has shown to also increase testosterone levels in men with type two diabetes mellitus, however, the use of metformin in this cohort of patients has been shown to reduce testosterone levels and prevent the beneficial effect that an improved glycaemic control has on testosterone levels.

The effect of testosterone therapy in men with Type 2 diabetes mellitus and metabolic syndrome has been extensively studied. A comprehensive review of the topic was conducted by Hackett [29] in 2019. Results show that testosterone had a beneficial effect on glycaemic control, sexual dysfunction, body composition, lipid profile, anaemia, and bone density. However, there were arguments for both increased and decreased cardiovascular risk. A follow-up report on prediabetic and diabetic women from the Outcome Reduction with an Initial Glargine Interventional Trial looked at baseline testosterone and SHBG as predictors of cardiovascular events and mortality over six years.[30] When adjusted for age and cardiovascular risk factors, both free and total testosterone were not associated with any outcomes. Baseline SHBG was not associated with cardiovascular events but did show increased all-cause mortality when adjusted for age (hazard ratio [HR] 1.15; 95% CI 1.06 to1.24; *p*<0.01) and other cardiovascular risk factors (HR 1.14; 95% CI 1.05 to 1.24; *p*<0.01).

Testosterone also improves weight loss and physical fitness in HIV-positive men and men suffering from cancer cachexia.[31]

Testosterone and inflammation

Numerous cells involved in inflammation possess the androgen receptor and androgens have been shown to have an anti-inflammatory effect in several conditions of chronic inflammation.[1] Testosterone therapy decreases proinflammatory cytokines in conditions of chronic inflammation.[32] This occurs as testosterone prevents nuclear translocation of NF-κB (which induces the expression of various proinflammatory genes encoding cytokines and chemokines), blunts the increased production of proinflammatory mediators caused by interferon-γ (INF- γ),[32] decreases prostaglandin E2 (PGE2) production and prevents maturation of type-1 and type-17 helper T cells.[33] Testosterone also modulates inflammation by altering leukocyte infiltration,[34-36] preventing the deleterious effect of interleukin-1β (IL-1β) and IL-6 on cartilage and bone, attenuating the expression of vascular cell adhesion molecules,[7] and by promoting angiogenesis which assists in the resolution of inflammation and wound healing.[36]

Some studies suggest that testosterone has a proinflammatory effect. This results from an increase in oxidative stress, caused by increased production of reactive oxygen species (ROS), and by an increased expression of certain chemokines. Testosterone increases ROS production by enhancing the activity of the enzyme NADPH oxidase,[37] reducing the activity of antioxidant enzymes,[37] and increasing levels of toll-like receptors (TLRs).[38] It must be noted that these studies used large doses of testosterone (up to 10 mg/kg per week) in their research. Animal models of myocardial ischaemia have shown that testosterone promotes inflammation by increasing the expression of signalling proteins associated with myocardial ischaemia.[39] Studies have shown that long-term testosterone therapy neither decreases nor increases markers of inflammation in elderly hypogonadal men and post-menopausal women.[40,41]

Studies examining the effect of androgens on inflammation in critical illness are limited. Animal studies show that androgen deficiency, or androgen receptor blockade, preserves the immune response to critical

illness by maintaining cell-mediated immunity, which includes the release of proinflammatory cytokines.[42] However, studies addressing the effect of testosterone therapy on inflammation during critical illness show that it may be proinflammatory, by increasing activation of the p38 mitogen-activated protein kinase signaling pathway.[43]

There are currently no human studies investigating the effect of testosterone therapy on inflammation in critical illness, however testosterone therapy has been shown to attenuate the increase in IL-6 ($p = 0.042$) and CRP ($p = 0.043$) seen in men undergoing coronary artery stenting.[44] Contrary to this, the relationship between sex hormone measurements after trauma and clinical outcomes has shown that elevated testosterone levels within 24 hours after injury are associated with elevated IL-6 levels ($p = 0.015$ at 6 hours, $p = 0.004$ at 24 hours); and that rising testosterone levels between 6 and 24 hours were associated with higher odds of multiple organ failure ($p = 0.02$) and nosocomial infections ($p = 0.03$).[45] A review by Angele et al on the sex differences in sepsis showed that male gender was associated with a higher sepsis incidence in surgical patients and that premenopausal females tolerated a septic insult better than males. [46]

Testosterone therapy in the critically ill patient
Acute critical illness
Our search identified fourteen articles (four animal, ten human) related to the use of testosterone in the acute phase of critical illness. The animal studies showed conflicting results as two studies demonstrate that androgen deficiency has a beneficial effect on myocardial function in trauma subjects and improves mortality in septic subjects.[47,48] However, the remaining two studies suggest that testosterone supplementation may improve survival in subjects with sepsis and nitric oxide synthase deficiency; and that testosterone therapy attenuates cerebral vasospasm in cases of subarachnoid haemorrhage.[49,50]

Human studies are sparse, but a clear benefit is seen in patients suffering burn injuries. Oxandrolone therapy among burn patients has been shown to improve mortality,[51,52] improve lean body mass,[53] reduce healing time of donor sites,[54] and reduce the length of hospital stay.[55] Two studies assessing the use of oxandrolone in trauma patients did not show promising results as these patients had a longer duration of mechanical ventilation, and higher reintubation rates and oxandrolone did not improve the length of ICU or hospital stay.[56,57] Table 2 summarises the articles related to the use of testosterone in human patients with acute critical illness.

Recovery after acute critical illness
Our search identified 28 articles related to the use of testosterone in the recovery phase of critical illness. As hypotestosteronaemia can persist well into the recovery phase of critical illness, Ward et al.[58] developed a screening tool to detect hypotestosteronaemia in cardiothoracic surgery patients. Their screening tool identified patients who were older than 18 years, admitted to the ICU for longer than seven days, post cardiothoracic surgery, at risk for malnutrition and with poor mobility. The screening tool identified 13 men and seven women. Total testosterone levels were subsequently measured and all 13 men had hypotestosteronaemia, while only three of the seven women had hypotestosteronaemia.

There is a large body of research looking at the effect of androgens, particularly oxandrolone, in the management of burn patients. Paediatric studies have shown that oxandrolone preserves lean body mass by increasing muscle protein synthesis and myosin and tubulin gene expression in skeletal muscle.[59] When combined with exercise, oxandrolone therapy results in an even greater positive change in

lean body mass and strength.[60] Long-term treatment of paediatric burns patients with oxandrolone not only resulted in improved lean body mass at 12 months after burn injury but also improved bone mineral content, bone mineral density and reversed growth arrest.[61,62] Markers of lung function, such as maximum voluntary ventilation and maximum expired ventilation are also improved by long-term oxandrolone therapy.[63]

Research in adult burn patients shows that oxandrolone, combined with adequate nutritional intake, reduces weight loss and daily nitrogen loss in the recovery phase of severe burn injuries by decreasing muscle protein breakdown.[64,65] It has also been demonstrated that oxandrolone improves the rehabilitation of these patients by increasing weight gain up to three times faster compared with nutritional support alone. This weight gain was maintained after oxandrolone discontinuation.[65]

As physical rehabilitation alone has failed to improve ICU-acquired weakness, testosterone has been considered a therapeutic option to treat or prevent muscle wasting and weakness in this cohort of patients.[66-69] Most of these studies extrapolate findings from studies on burn patients in which oxandrolone therapy has been shown to improve lean body mass. A systematic review of 70 trials by Tomassini et al.[70] investigated interventions to address sarcopenia in a surgical population. Testosterone exerts its anabolic effect on muscle through the androgen receptor, increasing gene transcription and leading to an increase in protein synthesis and a decrease in catabolism. Testosterone also increases the expression of IGF-1, an important growth factor that regulates skeletal muscle anabolism.[67] Testosterone also has an anti-catabolic effect through the inhibition of the nuclear factor-kB-inducing kinase (NIK) pathway which is both proinflammatory and plays a role in skeletal muscle atrophy.[71]

The GAINS trial was a pilot randomised controlled trial assessing the effect of nandrolone on 22 patients recovering from critical illness weakness.[72] The primary outcome showed that nandrolone therapy resulted in an insignificant increase in median grip strength ($p=0.185$) and a significantly lower muscle strength sum score ($p=0.001$) from baseline. It must be noted that the placebo group received more calories, protein and physiotherapy. The secondary outcomes showed that nandrolone therapy resulted in fewer hours of mechanical ventilation ($p=0.032$), a shorter length of ICU stay ($p=0.065$), a shorter length of hospital stay ($p=0.023$) and a better ICU mobility score on discharge ($p=0.005$). The differences in ICU readmission rate, ICU survival and 90-day survival were insignificant.

The use of testosterone to improve recovery in orthopaedic patients has also been investigated. A review by Weber et al.[73] showed that testosterone therapy after total joint arthroplasty can reduce the length of hospital stay, improve muscle strength, aid in-hospital rehabilitation and improve functional mobility.

Discussion
The onset of acute critical illness in men causes hypotestosteronaemia similar to primary hypogonadism. Hypotestosteronaemia persists during the recovery phase but then mimics secondary hypogonadism. There is evidence to suggest that testosterone levels at the onset of critical illness are inversely proportional to the severity of disease and may be predictive of mortality, length of ICU stay and need for mechanical ventilation. Testosterone has an anti-inflammatory effect in conditions of chronic inflammation, but the physiological effects of testosterone during acute inflammation are unclear.

Some studies show that hypotestosteronaemia or androgen receptor blockade, during acute inflammation, preserves the immune response

Table 2. Human studies investigating the use of testosterone in acute critical illness

Study	Cohort / Number of patients / Design	Objectives	Outcome
Pham et al[51]	• Adult burns • 117 • Multicentre observational	To assess the effect of oxandrolone therapy on acute hospitalisation outcomes in severely burned patients.	Patients receiving oxandrolone underwent more operations (*p*=0.36), were ventilated for longer (*p*=0.75) and had a longer ICU length of stay (*p*=0.26). However, they were transfused fewer units of blood (*p*=0.93), developed fewer nosocomial infections (*p*=0.38), had less multiple organ dysfunction (*p*=0.11) and had a lower mortality rate (*p*=0.01). It must be noted that the patients receiving oxandrolone had a higher mean percent full thickness injury (*p*=0.12).
Altarrah et al[52]	• Adult burns • 52 • Retrospective analysis	To assess the effects of corticosteroid and oxandrolone therapy on mortality, multi-organ failure and sepsis in patients with acute burns.	Oxandrolone treatment showed reduced odds of 28-day mortality (OR 0.11, 95% CI: 0.04 to 0.3), in-hospital mortality (OR 0.19, 95% CI: 0.08 to 0.43) and sepsis (OR 0.24, 95% CI: 0.08 to 0.69). However, oxandrolone treatment was associated with increased odds of multi-organ failure (OR 7.9, 95% CI: 2.89 to 21.6).
Jeschke et al[53]	• Paediatric burns • 235 • RCT	To assess the effect of oxandrolone therapy on clinical parameters, body composition, serum hormones and cytokines in the acute post burns phase.	Oxandrolone-treated patients had a shorter ICU stay (*p*=0.4), needed fewer operations (*p*=0.7), had a shorter duration between operations (*p*=0.037) and had fewer incidences of infection (*p*=0.7). However, mortality was higher among the oxandrolone-treated patients (*p*=0.7). Patients receiving oxandrolone had a significantly improved lean body mass (*p*<0.05), serum testosterone levels (*p*<0.05) and reduced acute phase proteins (*p*<0.05).
Demling et al[54]	• Adult burns • 20 • RCT	To investigate the effect of oxandrolone on nitrogen balance, body weight and donor site healing in severely burned patients.	Net weight loss, nitrogen loss and healing time of the donor sites were all significantly less in the oxandrolone group (*p*<0.05).
Wolf et al[74]	• Adult burns • 81 • RCT	To investigate the effect of oxandrolone therapy on clinical outcomes in severely burned patients.	Oxandrolone therapy resulted in a reduced length of hospital stay (*p*<0.05), reduced duration of mechanical ventilation (*p*=0.282), fewer surgical procedures (*p*=0.015), more patients being discharged to home (*p*=0.375) and reduced hospital charges (*p*=0.623)
Cochran et al[75]	• Adult burns • 167 • Practice-based evidence study	To investigate the relationship between oxandrolone therapy and length of hospital stay in burned patients.	Oxandrolone therapy resulted in a shorter length of hospital stay (*p*=0.03).
Ferrando et al[76]	• Adult burns • 6 • Pre- and postinterventional trial	To assess the effect of testosterone on muscle protein metabolism in severely burned patients.	Testosterone treatment resulted in increased protein synthesis efficiency (*p*<0.01), decreased protein breakdown (*p*<0.05), and an improved net amino acid balance (p <0.0001).
Ring et al[55]	• Adult and paediatric burns • 2367 • Systematic review and meta-analysis	Primary outcomes included the effect of oxandrolone on mortality, length of hospital stay and liver dysfunction in severely burned patients. Numerous secondary outcomes.	Oxandrolone treatment resulted in a significant reduction in the length of hospital stay (*p*=0.01). There was an insignificant effect on the incidence of liver dysfunction (*p*=0.88) and mortality (*p*=0.42).
Bulger et al[56]	• Adult trauma and surgical • 41 • RCT	To investigate the effect of oxandrolone on duration of ventilation, reintubation, length of stay and mortality among ventilator-dependent surgical patients.	Patients receiving oxandrolone required more days of ventilation (*p*=0.03), had a higher reintubation rate (*p*=0.02), had a longer ICU stay (*p*=0.09) and spent more days in hospital (*p*=0.84). Mortality was higher in the placebo group (*p*=0.14).
Gervasio et al[57]	• Adult trauma patients • 60 • RCT	To investigate the effect of oxandrolone therapy on nutritional and clinical outcomes in the first month following multiple trauma.	Oxandrolone therapy did not have any significant benefit on nitrogen balance (oxandrolone: -3.8 g/day +/-10.6, placebo: -6.3 g/day +/-12.5), length of hospital (oxandrolone: 30.8 days +/-17.9, placebo: 27 days +/-25.7) and ICU stay (oxandrolone: 17.1 days +/-7.8, placebo: 12.6 days +/-10) or frequency of sepsis (oxandrolone: 21 patients, placebo: 22 patients).

ICU = intensive care unit; OR = odds ratio; CI = confidence interval; RCT = Randomised controlled trial.

and is associated with increased levels of proinflammatory cytokines. However, it has also been proven that elevated levels of testosterone within the first 24 hours after trauma are associated with higher IL-6 levels and a rising testosterone level between 6 and 24 hours is associated with higher odds of multi-organ failure (MOF) and nosocomial infection. The cytokine response to critical illness is what leads to MOF.[77] Androgen receptor blockade, to preserve the immune response in critical illness, therefore appears inappropriate.

Testosterone is metabolised into oestrogen which is known to have an anti-inflammatory effect. The question therefore arises, does testosterone modulate acute inflammation through its effect as an androgen or its effect as oestrogen? One would expect studies investigating the effect of DHT, which does not undergo aromatisation, to provide clarity on this issue, but both DHT therapy and 5α-reductase inhibition (which inhibits DHT synthesis) have been shown to have an anti-inflammatory effect during acute inflammation.

Animal studies on acute trauma and sepsis have shown varying results. Testosterone deficiency[47,48] and testosterone supplementation[49,50] have both been shown to have beneficial effects. Testosterone therapy in cases of acute trauma and sepsis may worsen the outcome by contributing to hypotension, and therefore impaired organ perfusion through its non-genomic effects on the vasculature.

Burn victims seem to be the only cohort of patients in which testosterone therapy has shown benefit in both acute and chronic critical illness. In the acute phase, improvements are seen in mortality, healing time of donor sites, septic events and lean body mass.[51-57] In the recovery phase oxandrolone therapy, physical exercise and adequate nutritional intake have been shown to reverse growth arrest and improve both body composition and lung function.[59-65]

Previous studies addressing the effect of testosterone on mechanical ventilation showed conflicting and statistically insignificant results.[51,56,57] No study has identified testosterone therapy alone as the solution to treat ICU-acquired weakness.[66-68,70,71] The GAINS Trial has shown that testosterone therapy, in patients recovering from critical illness, results in a statistically significant reduction in the duration of mechanical ventilation, as well as improvements in length of ICU stay and ICU mobility score.[72] A notable difference of the GAINS trial is its focus on physiotherapy and not just the nutritional intake of its patients. Future studies on testosterone and ICU-acquired weakness should emphasise physiotherapy to reap the greatest benefits of testosterone's anabolic effect.

Given that the effects of testosterone on acute inflammation are not fully understood and that testosterone is known to cause vasodilation, we would not recommend the use of testosterone in patients who are haemodynamically unstable or going through an acute septic event. Evidence does suggest that once the acute phase of critical illness has subsided, testosterone therapy may be beneficial in reducing the need for mechanical ventilation. The literature also suggests that testosterone may be a valuable tool in treating ICU-acquired weakness and improving the functional activity of patients undergoing physical rehabilitation after surviving critical illness. However, larger studies are needed to confirm these findings. We also recommend that healthcare providers consider routine screening for hypotestosteronaemia in chronic critically ill patients and refer patients who survive critical illness to a multidisciplinary rehabilitation team, which may include testosterone therapy combined with physiotherapy and adequate nutritional intake.

An interesting avenue of research would be to determine the effect of using testosterone preoperatively, to improve physical status, on the clinical outcomes of patients undergoing major elective surgery.

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