Influence of physiological androgen levels on wound healing and immune status in men

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Abstract
Aging in men is associated with a progressive decline in the production of several hormones, including androgens. The extent to which an age-dependent decline in androgen levels lead to health problems or can affect quality of life remains under debate. Clinical results on replacement therapy do not yet provide a definitive clue on the benefit/risk balance. A sexual dimorphism of the immune system is well established, and the differences between female and male immune responses under normal, as well as pathological, conditions are generally attributed to the influence of estrogens, progestins, and androgens. The suppressive effects of male sex hormones on immune functions have been observed in a wide variety of disease processes and appear to be testosterone-mediated. Endogenous testosterone inhibits skin wound healing response in males and is associated with an enhanced inflammatory response. Although there are no known gender-related differences in permeability barrier function in adults, estrogens accelerates—whereas testosterone retards—barrier development in fetal skin, and male fetuses demonstrate slower barrier development than female littermates.

Keywords: Aging, wound healing, androgens

Introduction
Male aging is associated with a progressive decline in androgen production. The physiological causes for this phenomenon seem to be multifactorial. Some data exist on the magnitude of the decrease in adrenal androgens with age and the prevalence of older male individuals with low testosterone levels. Belanger et al. [1] reported on a marked decrease in dehydroepiandrosterone (DHEA) formation by the adrenals, which leads to a decrease of about 50% in total androgens in men between the ages of 40 to 80 years. The extent to which an age-dependent decline in androgen levels leads to health problems, or can affect quality of life, is under investigation [2–5]. In men older than middle-age, total testosterone levels alone may be misleading and the increased sex hormone-binding globulin levels have to be considered in parallel. The mechanism of the age-associated decrease in androgen levels leads to health problems, or can affect quality of life, is under investigation [2–5]. In men older than middle-age, total testosterone levels alone may be misleading and the increased sex hormone-binding globulin levels have to be considered in parallel. The mechanism of the age-associated decrease in endocrine testicular function is essentially due to primary testicular failure, but important changes also occur at the hypothalamicpituitary level. The most prominent endocrinological alterations with regard to male aging are related to the gonadal and the adrenal hormones—DHEA/DHEA sulphate and androstenedione—but others, such as growth hormone, insulin-like growth factor 1, melatonin, cortisol, and thyroxine are also affected [6–8]. In a subset of aging male plasma testosterone, levels fall below a critical level resulting in hypogonadism. This state of testosterone deficiency has an impact on bone, muscle and brain function, and is possibly a factor inducing the accumulation of visceral fat associated with an increased risk of non-insulin-dependent diabetes mellitus [9] and cardiovascular diseases.

It is therefore probable that androgen replacement to selected male individuals with proven androgen deficiency may have beneficial effects. The major goal of androgen substitution is to replace testosterone at levels as close to physiological levels as possible. For some androgen-dependent functions, testosterone is a pro-hormone, peripherally converted to 5α-dihydrotestosterone (DHT) and 17β-estradiol (E2), of which the levels should preferably be within physiological range. Natural testosterone is viewed as the best androgen for substitution in hypogonadal men. The reason behind this selection, however, is that testosterone can be converted to DHT and E2, thus developing the full spectrum of testosterone activities in long-term substitution. Recent insights imply that estrogens also fulfil a significant role in men. A major disadvantage of natural testosterone substitution is the strongly fluctuating levels of plasma testosterone, which are not in the physiological range at least 50% of the time. Also, the generated plasma E2 is usually supraphysiological. Administration of testosterone to young individuals has almost no adverse effects. With increasing age the risk of adverse effects increases.
effects on the liver, lipid profile, cardiovascular disease, prostate [10–12], sleep disorders [13–16] and emotional behavior increases. The following review will address the relevance of normal testosterone levels in aging males and the potential role of androgen administration in wound healing, immune status and epidermal permeability barrier homeostasis of aging men.

Age-related decline of androgen levels

Terms like male menopause or andropause more or less suggest that, similarly to women, all men go through a profound decline of their androgen production from middle age on. However, it should be stressed that the age-related decline of androgens in male follows a totally different pattern in comparison to the menopause. Several studies have shown that plasma testosterone, and in particular free testosterone, decreases with aging. Initially, cross-sectional studies [17–19], but also more recent longitudinal studies [20], have documented a statistical decline in plasma testosterone by approximately 30% in healthy men between the ages of 25–75 years. Harman et al. [21] showed data indicating that as many as 75% of all men are hypogonadal by the time they reach the age of 80 years – and 50% of men over the age of 65 years meet the endocrine criteria for hypogonadism. Apart from the recommendations of Morales and Lunenfeld [23], stringent criteria for testosterone deficiency have not yet been formulated. In a study of 300 healthy 20–100-year-old men, Vermeulen et al. [19] defined the reference range of testosterone to be between 11 nmol/l and 40 nmol/l. The authors found only one man with subnormal testosterone levels in the 20–40 year age group, but found that more than 20% of participants over the age of 60 and 15% of participants over the age of 80 still had testosterone levels above 20 nmol/l. The implication of this is that the fall of testosterone levels below normal is not universal in men, but affects only a certain proportion. The term “partial androgen deficiency of the aging male” (PADAM) has been proposed to describe this phenomenon. The androgen deficiency is partial in two ways: (1) the decline in androgen levels is not as profound as the decline of estrogens in menopausal; and (2) it affects only a proportion of aging men, increasing with age.

Wound healing

Aging and wound healing

Impaired wound healing leads to substantial morbidity and mortality of the elderly, as well as increased costs to health services [24]. Although the process of wound healing is a continuum, it is classically separated into a series of overlapping phases. These four phases (hemostasis, inflammation, proliferation and resolution) have been studied in detail and exhibit characteristic changes with aging. Decreased levels of growth factors, diminished cell proliferation and migration, and reduced extracellular matrix secretion have been demonstrated [25]. Impaired age-related wound healing states—involving both acute wounds that fail to heal and chronic ulcers—are characterized by excessive leukocytosis and subsequently enhanced proteolytic degradation of matrix constituents [26,27]. In addition to intrinsic aging per se causing delayed healing, studies have suggested marked gender differences in wound repair. Reports have shown that men heal acute wounds more slowly than women and also have an altered inflammatory response. Older epidemiological studies have not reported any impact of gender on wound repair; however, recent studies have demonstrated that the male genotype is a strongly positive risk factor for impaired healing in the elderly [28–30]. By analysis of acute wound tissue from health status-defined subjects, Ashcroft et al. [31] showed that collagen VII deposition was dramatically reduced with increasing age, particularly in elderly men. In concordance with animal studies, wound tumor necrosis factor (TNF-α) levels were shown to increase with age on day 7 after wounding, with a marked increase in macrophages staining positively in the wounds of elderly males.

Whereas sustained systemic and local estrogen levels in both young females and males may contribute to reduced inflammation via direct effects on cell adhesion molecule expression, the absence of such protective anti-inflammatory action in the elderly may correspond to increased inflammation and TNF-α expression. Moreover, in elderly men, reduced estrogens coupled with maintained levels of bioactive testosterone results in a failure to dampen the TNF-α response. Intriguingly, reversal of age-related impaired healing can be achieved in both animal and human models with topical and systemic estrogens, associated with a downregulation of neutrophil L-selectin and a dampened inflammatory response [29]. Beyond the age-related modulation of specific subsets of inflammatory cells, the responses of individual cells also appear to alter with the age of the donor. It has been reported that stimulated mononuclear cell production of the pro-inflammatory interleukin (IL)-6 and TNF-α and spontaneous IL-6 production are increased in cells from human donors [32].

Wound healing and estrogens

The skin appears to act as an end-organ target for estrogogenic action. Marked structural and functional skin changes occurring after the menopause can be related to altered hormonal profiles. One of the most important consequences of such hormonal changes is the age-related delay in cutaneous wound healing. Reduced estrogen levels have major downstream effects on cellular and tissue responses to injury; such
downstream effects include impaired cytokine signal transduction, unchecked inflammation and altered protein balance, and have a major impact on the rate of wound healing. Local levels of bioavailable estrogens are altered in the elderly due to a combination of decreased circulating gonadal estrogens (particularly important in postmenopausal females) and markedly reduced levels of the adrenal sex steroid precursor DHEA, resulting in a parallel decrease in androgen and estrogen formation from DHEA aromatization in peripheral tissues [33–35]. Estrogens can reverse age-related impaired healing in females when applied topically or given systemically, and is associated with reduced local inflammation and enhanced matrix deposition. In 1997, Ashcroft et al. showed that ovariectomized young female rodents exhibited a marked delay in repair of acute incisional wounds, which was reversed by the topical application of estrogens. The cellular mechanism underlying these changes involved an estrogen-induced increase in latent tumor growth factor-ß secretion by dermal fibroblasts [36]. Ashcroft et al. have investigated the effects of topical estrogens on cutaneous wound healing in healthy elderly men and women, and related these effects to the inflammatory responses and local elastase levels, an enzyme known to be upregulated in impaired wound healing states. Eighteen health status-defined females (mean age 74.4 years) and 18 males (mean age 70.7 years) were randomized in a double-blind study to either active estrogen patch or identical placebo patch attached for 24 hours to the inner upper arm, through which two 4-mm punch biopsies were made. The wounds were excised at either day 7 or day 80 postwounding. Compared to placebo, estrogen treatment increased the extent of wound healing in both males and females, with a decrease in wound size at day 7, increased collagen levels at days 7 and 80, and increased day 7 fibronectin levels. Estrogen treatment was associated with a decrease in wound elastase levels secondary to reduced neutrophil numbers, and decreased fibronectin degradation. In vitro studies using isolated human neutrophils indicated that one mechanism underlying the altered inflammatory response involves both a direct inhibition of neutrophil chemotaxis by estrogens and an altered expression of neutrophil adhesion molecules [29].

Estrogens can reverse age-related impaired wound healing in human and animal models, characterized by a dampened inflammatory response and increased matrix deposited at the wound site. Macrophage migration inhibitory factor (MIF) is a candidate proinflammatory cytokine involved in the hormonal regulation of inflammation. Ashcroft and colleagues demonstrated that MIF is upregulated in a distinct spatial and temporal pattern during wound healing, and its expression is markedly elevated in wounds of estrogen-deficient mice as compared with intact animals. Wound-healing studies in mice rendered null for the MIF gene have demonstrated that in the absence of MIF, the excessive inflammation and delayed-healing phenotype associated with reduced estrogens is reversed. Moreover, in vitro assays have shown a striking estrogen-mediated decrease in MIF production by activated murine macrophages, a process involving the estrogen receptor [37].

Wound healing and androgens

In elderly males, the response to estrogen is significantly reduced compared with that in females, suggesting that other, unknown, factors are involved beyond the effects of reduced estrogens. One factor that has not been investigated to date is the potential role of androgens in wound repair and local cutaneous inflammation. Elderly men generally maintain testosterone levels, albeit with a gradual reduction with increasing age, and androgens have been reported to be pivotal mediators of local and humoral immune responses in other pathophysiological processes.

In this context, several reports indicate that androgens play a critical role in the immune response and account for differences in outcome based on sex, including susceptibility to sepsis, parasitic infections, and atherosclerosis related to enhanced monocyte adhesion to endothelium [38–40]. Androgens have been related to both pro- and anti-inflammatory states at both the systemic level [41] and the cellular level, modulating IL-1, IL-2, and IL-6 in a variety of cell types including fibroblasts, macrophages (increasing IL-6), Kupffer cells (decreasing IL-6), splenocytes and osteoblasts [42–45]. Moreover, recent in vivo studies have suggested that castration of rats following burn injury significantly reduces systemic levels of proinflammatory TNF-α, and that the in vitro macrophage production of IL-1 and TNF-α is inhibited by androstenediol [46,47]. Taken together, these reports suggest that androgens may exert both anti- and proinflammatory effects that depend on the cell type, animal model and dose of treatment administered. In this regard, the role of androgens in the cutaneous wound healing response and the effects on local inflammation have not been thoroughly investigated.

Corroborative evidence for an inhibitory role for testosterone in the healing response came from an investigation concerning the relationship between wound area and systemic testosterone levels. In elderly men, there was a significant delay in repair with increasing testosterone levels, strongly implicating this hormone as a direct or indirect modulator of age-related wound repair. Systemic testosterone levels in elderly health status-defined human males strongly correlates with impaired healing of acute wounds. Gilliver et al. [48] reported that castration of male mice resulted in a striking acceleration of local cutaneous wound healing, which was also associated with a reduced inflammatory response and increased hair growth. Using a hairless mouse model, they...
demonstrated that testosterone reduction stimulated the healing response, not through hair follicle epithelial/mesenchymal cell proliferation, but directly via effects on wound cell populations. The mechanisms underlying the observed effects involved a direct effect of testosterone on murine macrophage, TNF-\(\alpha\), production via the androgen receptor (AR) in parallel to the in vivo downregulation of TNF-\(\alpha\) following castration or AR antagonism. Blockade of androgen action systemically, via AR antagonism, accelerates healing significantly, suggesting a specific target for future therapeutic intervention in impaired wound healing states in elderly males.

The sexual dimorphism of the immune response

Both experimental [49–56] and clinical epidemiological studies [57–63] have demonstrated the presence of a naturally occurring sexual dimorphism in the immune response to trauma, hemorrhage and sepsis, with significant advantages for women. During their reproductive years, females have a more vigorous cellular and humoral immune response than males as evidenced by a more developed thymus, higher immunoglobulin concentrations, and a greater ability to reject tumors and homografts and a better outcome from sepsis. Furthermore, evidence suggests that physiological levels of estrogens stimulate humoral and cell-mediated immune responses, while the male hormone testosterone does the opposite [64–66]. Whereas several studies have demonstrated the presence of AR in human and murine immune cells [67,68], recent findings also indicate that immune cells have the ability to directly metabolize sex steroids [69].

Investigation of Offner et al. [59] have shown that depressed cell-mediated immunity is reversed by castration or pharmacologic testosterone receptor blockade. Female rats, in contrast, showed enhanced immune function that was reduced to male levels by testosterone administration. This sexual dimorphism is believed to be responsible for the improved outcome in female mice following septic challenge. A five-year prospective cohort study confirmed that male gender is an independent risk for major infection after controlling for age and Injury Severity Score. Males had a 58% greater risk of developing a major infection. The authors concluded that male gender is associated with a dramatically increased risk of major infections following trauma.

Angele et al. [70] have implicated high testosterone and low E2 levels in the pathogenesis of immune suppression following trauma and hemorrhage using their well-established rodent model. Most recently, Schröder et al. [42] observed a marked reduction in hospital mortality among female patients with surgical sepsis (26% versus 70% in males). Cell-mediated immune response appears to exhibit sexual dimorphism. A century ago, it was observed that castration in adult male rabbits increased thymic mass, suggesting that sex hormones influenced the immune system. It has been proposed that maintenance of immune integrity in females following injury is due, at least in part, to the absence of immunosuppressive effects by androgens [71]. In a murine model of trauma-hemorrhage, Wichmann et al. [51] demonstrated that castration prior to injury prevented post-trauma immune depression. Castration two weeks prior to trauma-hemorrhage reduced plasma testosterone levels and preserved splenocyte IL-2 and IL-3 release compared with sham-operated animals. This laboratory also observed that pretreatment of female mice with DHT resulted in immunosuppression following trauma-hemorrhage similar to that occurring in males. The authors proposed that the balance between testosterone and E2 might be responsible for the immune depression seen in male mice post injury. Androgen has been shown to be responsible for producing immunosuppression in male mice [52,54]. Support for this notion comes from studies [40,52] that illustrated that depletion of male sex steroids by castration two weeks before trauma and hemorrhage prevented the depression of immune responses typically observed in normal males under those conditions. Similarly, administration of an androgen receptor blocker, e.g., flutamide, restored depressed immune responses and increased the survival rate of hemorrhaged animals subjected to subsequent sepsis [73,80]. Conversely, administration of physiological levels of androgen in female mice resulted in depressed splenic and peritoneal macrophage immune response following trauma and hemorrhage to levels comparable to those of males under those conditions [70]. Therefore, physiological levels of androgens suppress systemic cell-mediated immune responses in male mice following trauma and hemorrhage. Furthermore, this impairment has been associated with an increased release of proinflammatory cytokines and a decreased production of tumor growth factor-\(\beta\) at the wound site [81].

Both immunologic and physiologic parameters in animal models of trauma and hemorrhage have been examined, and a high estrogen-to-androgen ratio appears to be associated with an improved outcome [50–52,57,58,71,73–79]. Estrogen treatment restored the delayed-type hypersensitivity and splenocyte-proliferative responses, reduced macrophage IL-6 and increased survival after bacterial challenge. These studies suggested that estrogen treatment of injured male mice improves cellular immunity through direct modulation of NF-B activation [72]. In the laboratory, an increase in the ratio of estrogen to androgen, by either the appropriate receptor agonist or antagonist, has advantageous immunologic and physiologic effects. For example, male animals subjected to trauma and hemorrhage and then treated with E2 exhibit a restitution of immune and cardiovascular functions [74,75]. In addition, flutamide provided immune
and cardiovascular protective effects in male rodents subjected to trauma and hemorrhage, and conferred a survival advantage for male mice in which sepsis was induced 48 hours after hemorrhage [73,80]. In support of these data, improved immunologic and physiologic parameters have been reported for females in animal models of trauma and hemorrhage.

**The role of 5α-dehydrotestosterone (DHT)**

Several studies in mice indicated that, in particular, the most potent androgen DHT, suppress cytokine release by T cells and alter their cytokine profile [54,70,82,83]. Nitsch et al. [84] showed that precastration of mice prevented the significantly suppressed capacity of wound immune cells to release IL-1β and IL-6. In addition, precastration normalized the elevated IL-6 expression at the wound site in the trauma-hemorrhage mouse model. Moreover, wound-breaking strength was improved in castrated mice 10 days after trauma and hemorrhage. Because the percentage of macrophages and polymorphonuclear leukocytes within the wound immune cells was unaffected by trauma-hemorrhage or castration, the improvement in cytokine release in castrated animals was independent of distribution of wound immune cells. Similarly, depletion of DHT by castration restored the depressed cytokine release capacity of splenic and peritoneal macrophages following trauma-hemorrhage, whereas cell-mediated immune response in sham mice was not affected [50,52]. These findings suggested that physiological levels of testosterone were only harmful in an immunologically compromised host, not in normal animals. In this respect, it has been illustrated that steroid synthesis had been altered following hemorrhage [85,86]. Those studies demonstrated an increased DHT synthesis and a decreased catabolism of this steroid hormone following trauma-hemorrhage due to changes in the activity of enzymes involved in steroid synthesis. In particular, 5α-reductase activity was increased, whereas 17β-hydroxysteroid dehydrogenase activity was decreased following trauma-hemorrhage in lymphocytes and splenic macrophages harvested from male mice. Although steroid synthesis pathways in wound fibroblasts following hemorrhage have not been studied, the existing findings suggest that an enhanced intracellular DHT synthesis following trauma-hemorrhage may explain the immunodepressive effects of physiological DHT plasma levels. In this respect, suppressed wound immune cell cytokine release capacities following hemorrhage correlated with increased rates of wound infection [87]. Moreover, normalization of suppressed cell-mediated immune responses by androgen depletion decreased the susceptibility to subsequent polymicrobial sepsis [88]. Schneider et al. [89] supported the concept that androgens directly regulate macrophage functions after trauma and hemorrhagic shock. Both Kupffer cells and splenic macrophages possess intrinsic sex steroid synthesis capacity, because the 5α-reductase inhibitor 4-hydroxyandrostenedione (4-OHA) directly inhibited the effects of testosterone, but not DHT, on cytokine production. Moreover, inhibition of 5α-reductase enzyme activity, which converts testosterone to DHT, restored in vitro, as well as in vivo, macrophage immune responses after traumatic injury, indicating that DHT represents the crucial androgen that regulates macrophage cytokine release after traumatic injury [89–91].

**Epidermal permeability barrier homeostasis**

Sex hormones exert important influence on the late stages of permeability barrier development in utero [92]. Although there are no known gender-related differences in permeability barrier function in adults, estrogens accelerate whereas testosterone retards barrier development in fetal skin, and male fetuses demonstrate slower barrier development than female littermates. Moreover, prenatal administration of flutamide equalizes developmental rates in male and female fetuses [93]. A negative influence of androgens on skin development could explain ongoing outcome differences in premature human male versus female infants, even when treated with surfactant replacement therapy [94,95]. Kao et al. [96] evaluated the effects of changes in testosterone on barrier homeostasis in adult murine and human skin. Hypogonadal mice (whether by castration or by treatment with systemic flutamide) displayed significantly faster barrier recovery at 3, 6 and 12 hours than controls did, and testosterone replacement slowed barrier recovery in castrated mice. Moreover, testosterone directly affected the skin, as topical flutamide also accelerated barrier recovery in normal male mice. These findings appear to be of physiological significance, since prepubertal male mice (age 5 weeks) displayed accelerated barrier recovery in comparison with adult postpubertal (age 11 weeks) males. These studies also appear to be relevant to humans, as a hypopituitary human subject demonstrated repeated changes in barrier recovery in parallel with peaks and nadirs in serum testosterone levels during intermittent testosterone replacement [97]. Mechanistic studies showed that differences in epidermal lipid synthesis do not account for the testosterone-induced functional alterations. Instead, epidermal lamellar body formation and secretion both decrease, resulting in decreased extracellular lamellar bilayers in testosterone-replete animals. These studies demonstrate that fluctuations in testosterone modulate barrier function can have negative consequences for permeability barrier homeostasis. In addition, testosterone repletion affected adversely the kinetics of barrier recovery versus sham-operated controls [93]. Androgen depletion accelerated barrier recovery, and barrier function was enhanced significantly by either surgical or medical castration, indicating that these
observations were independent of the method of androgen depletion [93]. Androgen influenced not only barrier function, but also stratum corneum integrity, a measure of tissue cohesiveness. The functional differences in castrated versus sham-operated animals reflect changes in hormone levels that are within the normal-to-subnormal (hypogonadal) range. The physiologic relevance of these opposing outcomes in permeability barrier homeostasis was shown not only in prepubertal versus pubertal rodents, but also in humans.

Androgens also seem to be responsible for the detected gender-associated differences in cutaneous barrier function. Hanley et al. [93] demonstrated that cutaneous barrier formation, measured as transepidermal water loss, is delayed in male fetal rats. Administration of estrogen to pregnant mothers accelerated fetal barrier development both morphologically and functionally. In contrast, administration of DHT delayed barrier formation both in vivo and in vitro. Finally, treatment of pregnant rats with the androgen antagonist flutamide eliminated the gender difference in barrier formation. These studies indicated that: (a) estrogens accelerate and androgens delay cutaneous barrier formation; (b) these hormones exert their effects directly on the skin; and (c) sex differences in rates of barrier development in vivo may be mediated by testosterone.

Androgens are also more likely to be the mediators of gender differences in skin maturation. To determine if DHT, like estrogens, glucocorticoids, and thyroid hormone, directly affects the skin, fetal skin explants were incubated in the presence or absence of DHT. Epidermal water loss in treated explants was increased by ~25% after 3 or 4 days in culture [93]. Electron microscopy data revealed disorganized, unprocessed lamellar material in multiple layers of the stratum corneum interstices in explants incubated for 4 days with DHT. In contrast, control explants exhibited mature bilayers throughout the extracellular spaces of the stratum corneum, and unprocessed material was limited to the stratum granulosum–stratum corneum interface. Testosterone levels began to rise in the male fetal rats on day 16 of estimated gestational age [98], close to the time of onset of epidermal stratification. Hanley et al. [93] have demonstrated that the male fetus displayed a less competent barrier than the female on day 20 of estimated gestational age. Moreover, maternal administration of DHT caused a significant delay in barrier formation, suggesting that this gender difference is due to inhibitory effects by androgens. DHT, which did not aromatize to E2, appeared to have a direct effect on the skin, since the addition of DHT to fetal skin explants in vitro also delayed barrier maturation.

Moreover, gender may also influence the severity of diseases with abnormalities in skin barrier function. It is mentioned that severe atopic dermatitis and severe psoriasis occur more commonly in males than in females. Yet, the exact impact of gender on the severity of skin disease has not been studied systematically [99].

Conclusions
A sexual dimorphism of the immune system is well established, and the differences between female and male immune responses under normal, as well as pathological, conditions are generally attributed to the influence of estrogens, progestins, and androgens. The suppressive effects of male sex hormones on immune functions have been observed in a wide variety of disease processes and appear to be testosterone-mediated, as illustrated by numerous animal studies.

Endogenous testosterone inhibits the cutaneous wound healing response in males and is associated with an enhanced inflammatory response. Because decreasing androgen levels resulted in improved wound healing, the short-term treatment with flutamide following trauma-hemorrhage may similarly beneficially affect local wound immune cell function. Therefore, attempts to improve wound immune cell function at the wound site by treatment with AR blockers may represent a useful adjunct for improving wound healing and decreasing the incidence of wound infections in critically ill patients.

Estrogens are also critical mediators of wound healing accelerating repair in both human and animal models. The existing data demonstrate that topically applied estrogens, in both male and female subjects, can significantly diminish delay in wound healing in the elderly. There is convincing evidence to show that aromatization of androgens to estrogens is an important pathway for mediating the action of testosterone on skin physiology. Aromatase, localized to sebaceous glands and to both outer as well as inner root sheath cells of anagen terminal hair follicles, may play a “detoxifying” role by removing excess androgens [101]. Kung proposes that the major action of testosterone is mediated through aromatization to E2 and binding to the estrogen receptors and the balance between testosterone and E2 may be responsible for the immune depression seen in male mice after injury [101].

References
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