Dehydroepiandrosterone (DHEA): A Steroid with Multiple Effects. Is there Any Possible Option in the Treatment of Critical illness?

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Abstract: DHEA is the major circulating steroid in human blood and it is a central intermediate in the metabolic pathway of sex steroid hormone formation. Although the specific effect of DHEA is still unclear it was demonstrated that DHEA modulates several physiologic processes including metabolism and cardiovascular function. Furthermore, a profound immunomodulatory effect of DHEA was reported.

Several data demonstrate the beneficial effect of DHEA in situations of critical illness including trauma hemorrhage and sepsis. Accordingly DHEA improved the survival rate and physiological situation in several animal models of trauma hemorrhage and systemic inflammation. This effect was paralleled by profound changes of immunologic parameters, organ function, and heat shock protein production. Therefore, it was claimed that DHEA may be a new alternative/additive in the treatment of trauma and sepsis.

In line, DHEA is a frequently used drug in the field of anti-aging medicine, it is an over-the-counter drug in several countries, and it was reported that DHEA medication is free of major side effects. Therefore, DHEA could easily be used in a clinical trial investigating its effects in critical ill patients.

This article reviews the reported effects of DHEA on the base of the literature with the specific focus on trauma and sepsis/critical illness including its clinical perspectives.

DHEA: STRUCTURE AND PHYSIOLOGY

DHEA, 5-androsten-3β-ol-17-one, is principally a C-19 androgen classified with the adrenal androgens, androstenedione and testosterone [1]. The rate-limitating precursor in the synthesis of DHEA is pregnenolone and the DHEA-pathway therefore competes with that of glucocorticosteroids for precursor availability [2]. DHEA and its sulphated form DHEA-S are the most abundant circulating steroid hormones. Sources of DHEA production are the adrenal gland, the gonads and the brain [3-6].

More than 99% of the circulating DHEA is in the form of its sulphated ester DHEA-S and it was supposed that DHEA-S may be a kind of reservoir that can be converted into the biologically active form of DHEA [7]. DHEA is a primary precursor of important sex steroids and can be converted into estradiol and testosterone depending on the hormonal milieu [8-11].

The secretory pattern of DHEA is comparable to those of cortisol and DHEA ranks as an ACTH-regulated steroid hormone. However, other regulatory mechanisms have been proposed that modulate DHEA secretion independently of the HPA-axis [12,13]. Accordingly, in situations of stress or serious illness a dissociation of DHEA and cortisol levels were noticed with a metabolism away from DHEA and towards that of glucocorticoids [14].

DHEA and DHEA-S levels remain very low for the first years of live and start to rise with the puberty [15]. Plasma concentrations peak at the age of 20-25 and after this peak a decline of about 20% can be observed for every following decade ending up in values of 10% of the peak levels in the eights decade [16-21].

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GENERAL PHYSIOLOGICAL EFFECTS

The specific effect of DHEA and its physiologic relevance remains unclear and it was thought that the physiologic decline of DHEA was linked to a wide range of age related physiologic changes [22]. However, it was demonstrated that a DHEA deficiency state did not produce any gross symptoms [9]. A concept was introduced that DHEA may exert its effect only within particular physiologic settings or by antagonizing or buffering the effects of other hormones. However, previous investigations found a wide range of DHEA mediated physiologic effects [22-24].

DHEA and the Cardiovascular System

A possible protective effect of DHEA on the development of atherosclerosis was proposed since it was demonstrated that DHEA administration to rabbits with hypercholesterolemia led to an inhibition of plaque formation and aortic fatty streak formation [25,26]. In humans a protective effect of DHEA was noticed in a 12-years follow-up epidemiological study demonstrating a reduced cardiovascular risk of men displaying elevated DHEA-S levels [27,28]. This result was supported by data demonstrating an increased risk of coronary artery disease in men with decreased DHEA-levels [29]. More recent data demonstrate a gender difference of the DHEA effect with a positive effect of high DHEA levels in men but no effect in women [22]. However, other large and well designed studies found no or only a weak beneficial effect of high DHEA concentrations on the development of atherosclerosis [30,31].

DHEA and Metabolism

A modulation of metabolic processes was supposed to be a mechanism by which DHEA exert its protective effect on the cardiovascular system.

Animal studies demonstrated that administration of DHEA in mice induced a reduction of fat cell growth, weight

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gain, and lipogenesis. Accordingly a decreased differentiation of fibroblasts into adipocytes was noticed that was paralleled by a relatively increasing protein content of the body mass [32-35]. Specific mechanisms that were reported are a DHEA-induced inhibition of G6PDH activity and the increased activity of long-chain fatty acyl-coenzyme A hydrolase [36-38].

In addition to these animal studies several investigations were performed in human volunteers. The dosage of DHEA used in these studies ranged from 50mg /day to 1600mg/day given in a single or in repeated daily doses [39]. In line with their inhomogeneous designs these studies had inconsistent results. Using the high dosage of 1600mg/day a reduction of body fat was noticed in young men whereas DHEA administration in lower doses did not affect body fat in obese man or elderly women [40-42]. Correlations of serum DHEA or DHEA-S levels and parameters like body weight, body mass index, and percentage of ideal body weight displayed an inverse as well as a positive or no correlation with DHEA or DHEA-S levels [43-47].

Another effect that may contribute to metabolic changes related to the effects of DHEA was a modulation of serum insulin levels [48-50].

DHEA and Bone Mineralization

Another metabolic process that was discussed to be positively influenced by DHEA was bone mineralization. First it was noticed that in studies with primary cultured osteoblast-like cells from normal human bones that DHEA is converted to oestrone within these cells and may therefore contribute to the maintenance of bone mineral density in postmenopausal women [51]. It was further reported that DHEA may improve BMD of the distal radius and the femoral neck in elderly women [39]. However, the same investigators found that this effect was far smaller than that of established therapies for osteoporosis [39]. Other investigators found a positive correlation of DHEA-S and bone density in peri- and postmenopausal women. It was thought that DHEA may exert this effect by its conversion into estrogens in bone tissue [51]. In contrast to this exogenous DHEA administration failed to influence bone mineral density or markers of bone turnover in aging men and women [52,53].

DHEA and the Central Nervous System

Studies in rodents have shown that DHEA administration improved memory function in old mice [54-56]. Accordingly, it was suggested that DHEA may have an impact on cognitive functions although the results of human studies are controversial [57-59]. In Alzheimer patients elevated as well as decreased levels of circulating DHEA or DHEA-S have been reported [60-62]. Furthermore, DHEA plasma levels did not correlate to an impaired performance in cognitive function tests of older volunteers [63]. In line, no difference in DHEA concentrations was noticed between patients with dementia, and age-and gender-matched controls [64]. In contrast an improvement of mood and memory function was reported from a trial of DHEA treatment in elderly patients with major depression [65,66].

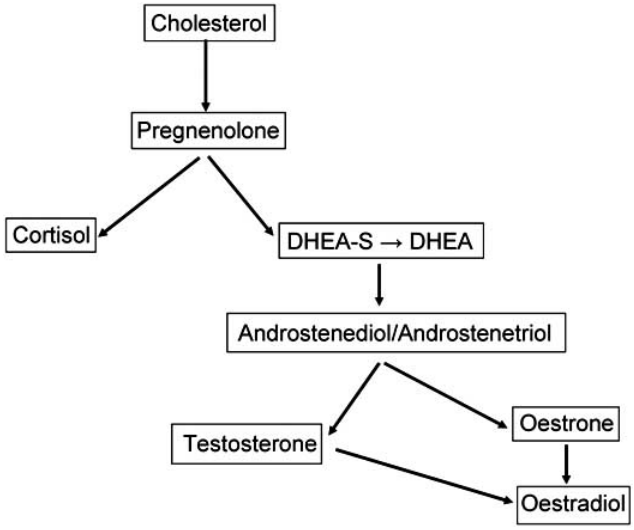

Fig. (1). Simplified diagram of DHEA-biosynthesis.

POTENTIAL SIDE EFFECTS

No data on the long-term safety of DHEA administration exists with respect to its potential side effects following administration in low (replacement therapy) or high and more "pharmacological" dosages. Most studies reported only mild side effects following DHEA therapy. It was noticed that DHEA led to a mild up to moderate but transient elevation of liver enzymes after a single oral dosage of DHEA [67]. A recent study about DHEA replacement in elderly women and men displayed no significant side effects [39].

A daily dose of 25-50 mg DHEA resulted in a 2-3 fold increase of serum androgen levels in women and increased oestrogen levels in men [24,66].

DHEA replacement decreased the disease activity in volunteers suffering from systemic lupus erythematosis and despite the high dosages of DHEA in this study only minor side effects like mild forms of acneiform dermatitis and hirsutism were observed [68,69]. Another side effect was an altered lipid profile with decreases of total serum cholesterol and serum triglycerides [22,24,70,71]. Up to now, several large and controlled clinical trials mostly dealing with DHEA administration in SLE-patients confirm that this treatment is not at risk of severe adverse events [13].

However, although there is no hint on serious adverse effects of therapeutic DHEA administration the safety of a long term therapy remains to be established [72].

GENERAL IMMUNOLOGICAL EFFECTS

The potential immunoregulatory role of DHEA was first shown decades ago. It was noticed that DHEA altered the cytokine production of activated T-lymphocytes and macrophages [73-78]. In addition, it was recently shown that cells of the immune system are capable to metabolize and convert DHEA into downstream steroids [79]. In line, lymphocytes

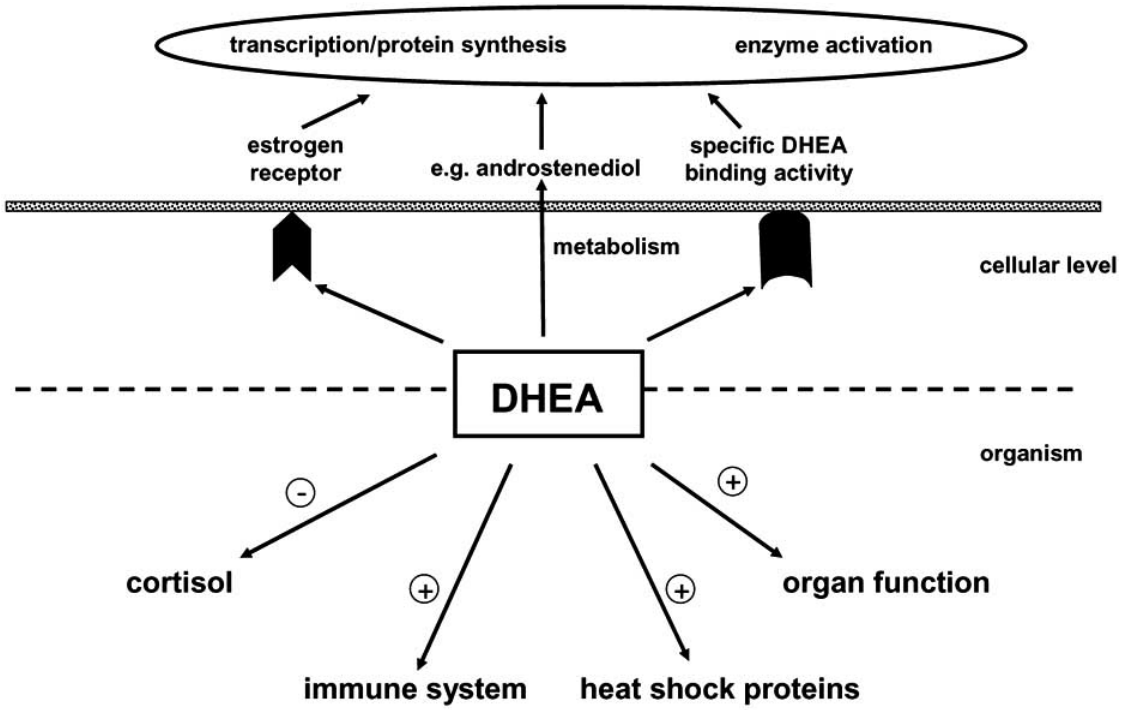

Fig. (2). Potential targets of DHEA with respect to the cellular level and the whole organism.

exposed to DHEA produced increased quantities of IFN-γ and IL-2, whereas the release of IL-4 was significantly decreased [76-78]. Accordingly, it was reported that DHEA enhanced IL-2 production by human peripheral blood T-cells stimulated *in vitro* [80]. These data were supported by the results of others reporting that DHEA represents a potent enhancer of IL-2 production by antigen- or mitogen-activated T-cells obtained from rodents or humans [76,80,81]. According to these results it was proposed that the primary immunologic target of DHEA may be the Th-1 subclass of the CD4+ T-cell population [80,81]. However, in contrast to this it was noticed that high doses of DHEA inhibited the proliferative response of T-cells *in vitro*, enhanced Th-2 response, and inhibited Th-1 mediated T-cell responses [74,82]. These observations were supported by another investigation demonstrating that DHEA may be an important factor for increasing Th-2 cytokine production (IL-10) and inhibited Th-1 and pro-inflammatory cytokine production (IL-1, IL-2, IL-6, interferon-γ, TNF-α) [75,83]. In addition, in an animal model of aging the age-related cytokine dysregulations were reversed by DHEA supplementation [84-86]. With respect to human studies it was reported that administration of DHEA in age-advanced men produced a "young-like" pattern of cytokine production and increased B-and T-lymphocyte proliferative activity [87].

That DHEA modulated T-lymphocyte activity was repeatedly demonstrated but with respect to the inconsistent data it is still not clear if this effect is accompanied by an inhibition or an activation of lymphocyte functions.

Furthermore, no data exit about the effect of DHEA on T-suppressor cells although this could be an important mechanism in modulating the homeostasis of the immune system.

Data about the effect of DHEA on B-lymphocyte function are rare. It was demonstrated recently that the *in vivo* administration of DHEA in mice affected B-lymphocyte function *via* a stimulation of IL-10 production [88]. It was also noticed that DHEA enhanced antibody production in mice either after immunization or after exposure to bacterial polysaccarides [89].

IL-2 production is a main target of glucocorticoids and it was assumed that DHEA may antagonize the glucocorticoid-induced decrease of IL-2 production and may therefore be immunostimulatory by antagonizing the immunosuppressive effects of glucocorticoids on the immune system [90-92]. In line, DHEA administration counteracted the inhibitory effect of glucocorticoids on IL-production of cultured T-cells [77]. Furthermore, DHEA failed to augment *in vitro* interferon-gamma production from T-cells but completely reversed the glucocorticoid-induced inhibition of interferon-gamma release [77]. Administration of DHEA in mice antagonized the dexamethasone-mediated suppression of B- and T-lymphocyte blastogenesis and thymus and spleen atrophy [91,93].

With respect to the results of a murine model of systemic viral infection the conversion of DHEA into more potent metabolites like androstenediol or androstenetriol was postulated to be a second mechanism that may mediate the DHEA-induced effects on the immune system. Furthermore, it was supposed that this mechanism may depend on the route of administration [94,95]. Furthermore, a direct receptor modulated way was discussed as a third way that mediates the DHEA-induced effects on immune cells. In line, the up-regulation of high-affinity DHEA-binding activity was demonstrated in activated human T-lymphocytes and the existence of a specific DHEA-receptor in murine T-cells was reported [96,97].

Several investigators demonstrated the beneficial effect of DHEA on immune function in the context of non-infective immunologic diseases. Administration of DHEA to mice suffering from experimental arthritis led to a reduction in the incidence and severity of the arthritis combined with a reduction of the IgG isotype autoantibody levels [98]. In another animal model with an experimental allergic encephalomyelitis in mice treatment with DEHA reduced the incidence and attenuated the severity of this disease. Furthermore, DHEA reduced the secretion of pro-inflammatory cytokines (IFN-γ, IL-12, TNF-α) and the NO-response. These effects were associated with a decrease in activation and translocation of NF-κB [99]. Concerning human studies it was demonstrated that DHEA administration was beneficial in patients suffering from systemic lupus erythematosus (SLE). A 12-month treatment trial with 200 mg DHEA per day reduced the frequency of disease flares and had an overall beneficial effect on disease activity in SLE. In several other diseases with autoimmunological background like rheumatoid arthritis, progressive systemic sclerosis or inflammatory bowel disease decreased plasma levels of DHEA were noticed and this led to the assumption that substitution of DHEA in these patients may be beneficial [77,100,101].

However, bearing in mind that the glucocorticoid-induced immunosuppression is one of the most sufficient treatment options in autoimmune diseases it is surprisingly that a steroid that is postulated to be immunostimulatory and that was demonstrated to antagonize the effect of glucocorticoids was also effective in the treatment of these kind of diseases. However, the main effect of DHEA was a restoration of the immunologic homeostasis. Therefore, during an autoimmune disease with an uncontrolled activation of immune cell functions DHEA may act synergistically to a glucocorticoid-induced immunosuppression in restoring a normal activity of the immune system and this may explain the beneficial effect of both steroids under these circumstances [90,93,98,99].

DHEA IN CRITICAL ILLNESS

Several studies investigated the immunomodulatory effect of DHEA during critical illness with all of these studies being performed in animals [102].

It was demonstrated that administration of DHEA to mice subjected to experimental sepsis increased the survival and improved the clinical situation (loss of body weight and body temperature) 48 hrs after induction of sepsis. This effect was paralleled by decreased serum TNF-α levels and an improved activity of T-cell-mediated immunity [103-106]. Another study that investigated the effect of DHEA in a combined model of trauma-hemorrhage followed by a subsequent sepsis reported a DHEA-induced increase of the survival rate 72 hours after induction of the septic insult (58% vs. 82%) [107].

Furthermore it was noticed, that DHEA improved cellular immune functions and preserved normal immunologic competence during systemic inflammation [104-108]. Accordingly, DHEA restored the depressed splenocyte proliferative activity, decreased splenocyte apoptosis rate, and increased the number of circulating NK-cells and CD8+-lymphocytes in septic rats [104-106,109]. It was further reported that DHEA decreased plasma IL-10, IL-6, and TNF-α concentrations and this was interpreted as a DHEA-induced attenuation of the systemic inflammatory response during sepsis [110]. In contrast to this it was noticed that administration of DHEA increased the TNF-α release of macrophages isolated from septic mice and that this effect was accompanied by an increased expression of toll-like receptor mRNA (TLR2 and TLR4) [111]. Another study concerning the effect of DHEA under the condition of systemic inflammation demonstrated that this effect did not depend on the expression of the TNF-receptor I [109]. However, it would be interesting to know if the type of infection (viral vs. bacterial) may influence the effect of DHEA on the release of cellular cytokines (e.g. Th1 vs. Th2 cytokines). With respect to the literature only few data are available about administration of DHEA following systemic viral infection. Most of these studies did not determine cytokine levels. Only one study reported mRNA concentrations (IL-10, IL-6, IFN-gamma) in cells of the eye and the central nervous system following an experimental encephalomyelitis induced by herpes-simples virus infection. Concerning these determinations an increase of IFN-gamma mRNA was found in both types of cells [94].

Several investigators demonstrated that the beneficial effect of DHEA during sepsis was related to profound alterations of cellular immune functions. However, in addition to this another mechanism was observed that could explain the effect of DHEA under the conditions of systemic inflammation. This mechanism was the DHEA-induced modulation of heat shock protein 70 (HSP-70) production during sepsis. It was demonstrated in a murine model of sepsis that DHEA augmented HSP-70 release in several target organs of septic shock (e.g. lung, spleen) [105]. Some investigators proposed that effect of DHEA during lethal bacterial or viral infections in mice may not be due to a direct effect of this steroid hormone but be due to a conversion of this DHEA into immunologically more potent metabolites like androstenediol and androstenetriol [95,112-114].

With respect to the current literature no human study is available investigating the effect of DHEA administration during sepsis. The only data available about DHEA and sepsis in humans investigated circulating DHEA concentrations in septic patients. These data demonstrate that decreased DHEA levels may be a prognostic factor in septic patients that indicates an exhausted adrenal reserve and may be associated with a worse prognosis [95,115,116]. In addition, an increased cortisol to DHEA ratio was reported and it was suggested that a decrease of DHEA and a relative increase of cortisol levels during sepsis may disturb the balance between glucocorticoid- and DHEA-mediated immune and vascular effects which may negatively affect the prognosis during septic shock [116,117]. The question arises from this if there is the need for a DHEA substitution in critical ill patients [118].

The effect of DHEA following trauma-hemorrhage was investigated in animal models using an experimental hemorrhagic shock [107,119]. Administration of DHEA in mice subjected to hemorrhagic shock restored the depressed splenocyte and macrophage functions 24 hours after hemorrhage

(increased IL-2, IL-1β, IL-6 release and improved splenocyte proliferation), normalized the sepsis-induced increase of splenocyte apoptosis, decreased the number of circulating CD8+ T-cells, and increased the CD4/CD8-ratio. The authors concluded that DHEA improved cellular immune functions in situations of trauma-hemorrhage [107,119]. Furthermore, it was reported that this effect may be due to a direct stimulatory effect on T-lymphocytes and due to a DHEA-induced prevention of a post-traumatic rise in serum corticosterone levels [120]. In addition to this it was noticed that DHEA improved the function of typical shock organs following traumatic shock. Accordingly, DHEA restored cardiac and hepatocellular function and prevented liver damage in a murine model of hemorrhagic shock and it was proposed that this effect may be directly mediated *via* the estrogen-receptors [121-123]. In contrast to this it was suggested by other authors that the beneficial effect of DHEA following situations of shock may be due to its conversion into androstenediol [124,125]. In addition to this it was further reported that the effect of DHEA following hemorrhagic shock may also be affected by factors like the gender and age of experimental animals [126-128].

Since it was proposed that DHEA is effective in restoring age related physiologic alterations including the so-called immune senescence it would be interesting to know if the effectiveness of the DHEA-induced immunomodulation changes with age. To our knowledge no experimental data are available that discriminate the effect of DHEA on immune functions during systemic inflammation or following trauma hemorrhage by the age. All recent experimental studies about DHEA and its effect during systemic inflammation or hemorrhage used middle-aged experimental animals. Therefore, on the base of the actual literature the question of the effectiveness of DHEA administration in patients of different age remains to be resolved.

Another factor that can be discussed is the gender of patients since it was proposed that gender and sex hormones may affect immune functions following sepsis and hemorrhagic shock. In line with this a gender dimorphic immune response has been reported after experimental sepsis and trauma hemorrhage. In this respect female animals subjected to sepsis or hemorrhage in the proestrus state demonstrated an increased survival and improved immune functions (decreased immune cell apoptosis, increased IL-1 release, improved splenocyte proliferation) compared to male animals. In line with this it was demonstrated that castration of male animals or testosterone administration to female animals attenuated cellular immune functions [126,129]. In extension to these data it was reported that this effect was blocked by administration of the estrogen antagonist Tamoxifen in-vitro. Therefore, it was concluded that DHEA may exert its beneficial effects due to a conversion into estrogens or by directly activating cellular estrogen receptors. It was proposed that administration of DHEA may be beneficial in male trauma patients whereas treatment with estrogens was supposed to be an option for female trauma patients [129,130]. In contrast to this it was reported that elevated estrogen levels in male and female patients suffering from critical illness or trauma are a predictor of death [131]. Currently, no data are available about the effect of DHEA in male or female patients suffering from trauma hemorrhage or sepsis. The question if DHEA restores organ function and cellular immunity in male or female patients to a degree comparable to those observed in experimental models of critical illness can not be answered. With respect to the literature most of the animal studies about DHEA and its effect during trauma and sepsis used male animals. However, even in female mice suffering from trauma hemorrhage an immunomodulatory effect of DHEA was demonstrated [126]. DHEA can be metabolized into estrogens as well as into androgens but the mechanisms regulating these pathways are still not understood although it was proposed that DHEA may predominantly be converted into estrogen under the conditions of a male hormonal environment [129,130]. The existence of the proposed gender dimorphism and its implication on therapeutic DHEA administration remains to be further established and it remains questionnaire if the metabolization into estrogens is the only or the most important way that mediates the observed beneficial effects of DHEA under the conditions of trauma hemorrhage or systemic inflammation.

CONCLUSION

DHEA is an inexpensive and readily available drug that is supposed to have only minor side effects. Although there are a large number of studies demonstrating the salutary effect of DHEA in animal models no data are available about the effect of DHEA in humans. Furthermore, several aspects of this treatment remain to be established, for example the effect of gender and age and the mechanisms underlying the observed beneficial effects of DHEA under the conditions of critical illness [72,126,129,130,132]. Therefore, clinical studies are necessary to establish whether this steroid hormone can be a new adjunct in the therapy of critical ill patients.

ABBREVIATIONS

BMP	=	bone morphogenetic protein
CD	=	cluster determinantes
DHEA	=	dehydropeiandrosterone
DHEA-S	=	dehydroepiandrosterone-sulfate
G6PDH	=	Glucose 6 phosphatdehydrogenase
HPA-axis	=	hypothalamus-pituitary-adrenal axis
HSP	=	heat shock proteins
ICAM	=	intercellular cell adhesion molecule
IL	=	interleukin
IFN	=	interferon
Ig	=	immunglobulin
NADPH	=	nicotinamidadenindinucleotidphosphat
NF-κβ	=	nuclear factor kappa-light-chain-enhancer
NK-cell	=	natural killer-cell
NO	=	nitrite oxide
PSA	=	prostate specific antigen
SLE	=	systemic lupus erythematosus

TLR = Toll like receptor

VCAM = vascular cell adhesion molecule

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