Is there a Potential Immune Dysfunction with Anabolic Androgenic Steroid Use?: A Review

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Abstract: Anabolic androgenic steroids (AAS) are artificial substances, acting through androgen receptors and were primarily developed for the treatment of hypogonadism, tumors, hypercalcemia, hypercalcuria and other chronic diseases. The discovery, in the early 1930s that these substances may have other benefits related to improvement in physique and athletic performance, has encouraged extensive use of these substances by amateur and professional athletes and members of the general public. The range of AAS used can be classified as either endogenous or exogenous. When used for ergogenic or recreational purposes the dosage is more often higher than the recommended dosage, and at supraphysiological levels, AAS can cause a number of serious side effects including liver dysfunction, myocardial infarction and potentially stroke, due to its ability to increase platelet and platelet aggregation. Furthermore, these high dosages may or can affect other physiological systems including the immune system. Hence, this paper reviews the current research on the effects of a number of specific AAS in the immune system.

Keywords: Anabolic androgenic steroids, immune system, cytokines, estrogen, T cells, testosterone.

INTRODUCTION

Charles Edouard Brown-Sequard was the first to observe significant enhancement in strength and energy following a dose of androgens extracted from animal testicles [1]. It was later observed that androgens were able to increase the growth of muscles, and improve the health of patients with chronic diseases, burns or trauma [2]. Anabolic androgenic steroids (AAS) are the most extensively used drugs among substance abusers [3, 4]. They are a class of synthetically manufactured substances classified as endogenous or exogenous substances that mainly exert their effects through binding on to androgen receptors. However, structural differences allow for further differentiation into 17-β hydroxyl testosterone esters, 17-α hydroxy alkyls and lastly those comprising a combination of the 17-β and 17-α.

Anabolic androgenic steroid usage is common amongst both amateur and professional athletes who have a tendency to use AAS ergogenically to enhance their performance [5]. However, a number of individuals in the general public may also utilise AAS for recreational purposes, for example to build muscle mass to enhance appearance [6]. It is estimated that in the USA 20% or 1-3 million people in the general population and 20-50% of professional athletes use AAS [7]. Clinically, most AAS have been used as treatment regimens for certain disorders [8, 9], nonetheless, in the absence of a therapeutic usage they may have adverse consequences on health [10]. Overuse and high doses of AAS have been associated with cardiovascular effects such as myocardial infarction and stroke [11, 12]. The excessive administration of AAS may have severe consequences on immune function as they may either over activate immune cell function or significantly dampen immune related activities.

To date there are many reviews on the use of AAS however they are limited studies reviewing the role of supraphysiological levels of AAS on immune function. Although little is known about the effects of AAS on the immune system, there are suggestions that when they are administered at supraphysiological concentrations, AAS can alter immune related cellular functions. Murine and *in vitro* studies demonstrate that at high doses AAS can decrease antibody sensitivity and secretion, cause a surge in the production of soluble proteins such as interleukin (IL)-1β, tumor necrosis factor alpha (TNF-α) and a decrease in IL-6, IL-2, IL-4, IL-5, interferons (IFN)s and corticotrophin secretion by peripheral lymphocytes [13-17]. Additionally, AAS was shown to suppress cell activity, importantly Natural Killer cell activity, and lymphocyte development into effector and memory cells [18]. Differing concentrations of testosterone for example, have been shown to affect neutrophil functions. In particular, testosterone at a dose of 10nM can reduce extra- and intracellular superoxide and increase phagocytosis [19], suggesting a decrease in the overall oxidative capacity of the neutrophils. Autoreactive immunity may develop affecting healthy cells, these autoreactive reactions can occur due to the adverse effects of certain drugs and may induce unfavourable consequences on immune cell function in particular T cells. It is known that androgens have anti-inflammatory effects and therefore in diseased states have been shown to modulate T cells, specifically, Cluster of differentiation $(CD)4^{+}$T cell pro-inflammatory cytokine production, inhibit T cell

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1389-5575/11 $58.00+.00

proliferation and expression of MHCII molecules on antigen presenting cells [20-24]. However, this may be potentially harmful in healthy individuals administering AAS at chronic concentrations. The purpose of this review is to identify the effects of AAS on the functions of the immune system specifically focusing on the $CD4^+$ T lymphocytes lineage as these cells are important in regulating anti- and pro-inflammatory episodes.

AAS

Anabolic androgenic steroids such as testosterone are important endogenous androgens normally secreted by the leydig cells of the testes following activation by luteinizing hormone. It can also be found in the circulation in either free form or bound to serum proteins. Under normal physiological conditions, testosterone is secreted and converted in to 5α-dihydrotestosterone or (DHT) 17β-estradiol in prostate and adipose tissue respectively. Only testosterone and DHT act through binding with high affinity to the androgen receptor. B-estradiol as the name implies binds to the estrogen receptor. The mechanism of AAS after intake in to the body can take many forms. In the body, testosterone exerts its effect through direct binding to the androgen receptors or reduction into DHT prior to binding and conversion in to β-estradiol [25]. However, testosterone is immediately metabolized in the liver, therefore, to prolong its effect and maintain it in circulation for longer duration derivatives of testosterone have been manufactured which can either be orally or intramuscularly administered.

AAS binds to the androgen receptor (AR) using the ligand–receptor binding interactions, AR changes its conformation where it undergoes dimerization, phosphorylation and shedding of heat shock proteins. A nuclear localization signal translocates the newly formed AR complex into the nucleus. In the nucleus, AR interacts with co-activators and also acts as a transcription factor targeting androgen response element sites upstream or downstream the location of the transcription start site of marked genes [26]. These genes are usually involved in the regulation of muscle mass and strength, bone formation, spermatogenesis, erythropoiesis, prostate and hair follicle formation [27]. A more indepth review of the AR signalling mechanism has been compiled by Bennett *et al*. [28]

T LYMPHOCYTES

The immune system is comprised of both the adaptive and innate systems, and the cells of both components interact to ensure physiological and immunological equilibrium. These cells also react with other proteins such as hormones and other peptides, for example AAS [29]. Cells of the immune system release certain proteins called cytokines and these are very important in regulating inflammation [30]. They can be characterised as either pro-inflammatory or anti-inflammatory proteins which control inflammation during either injury or immune insults. Supraphysiological levels of certain drugs can potentially cause immunological insults and thus either heighten or dampen the effects of these cytokines [31]. The T lymphocytes are important components of immunological function and are involved in the adaptive immune responses against antigens released during pathogen invasion or inflammation, and are recruited and activated *via* the release of soluble proteins by cells of the innate immune system, dendrtic cells, macrophages and neutrophils. The T lymphocyte population can be grouped in to two major types, $CD3^+CD4^+$ and $CD3^+CD8^+$. These recognise and selectively bind to peptides known as the 'major histocompatibility complex' (MHC), specifically MHC class II and MHC class I respectively [32].

$CD4^+$ T Helper Lymphocytes

Naïve $CD4^+$T lymphocytes differentiation into subtypes is dependent on signals received during initial antigen interactions. Upon activation by different transcription factors and in the presence of cytokines, $CD4^+$ T cell can differentiate advance into other subsets mainly T helper (Th) 1, Th2, Th17 and regulatory (Tregs) (Fig. **1**) [33]. Th1 and Th17 cells predominantly promote inflammation while Th2 inhibit inflammation and Tregs are suppressors of autoimmune reaction including autoreactive T lymphocytes that alter immune homeostasis. The mechanism of action of these cells occurs *via* the secretion and expression of transcription factors and soluble proteins (cytokines, chemokines and their receptors) [34]. Prevalence of Th1 and/or Th17 immune response reflects the occurrence or initiation of an autoimmune disease profile such as Rheumatoid arthritis and Multiple sclerosis [35, 36] moreover shift towards a Th2 mediated immune responses are observed in most systemic and allergic illness [37]. Tregs on the other hand tend to be elevated and super active in various cancers while the reverse is observed in autoimmunity [38, 39].

The Th1 cells primarily secrete IFN-γ IL-2 and lymphotoxin α (LTα) [40]. They are important in inducing effector responses against intracellular micro-organisms such as mycobacteria attack on immune function. IFN-γ fuels macrophages to phagocytose invading pathogens while the production of IL-2 is necessary for generating memory $CD4^+$ and $CD8^+$ T lymphocytes to aide in effective recognition and clearing of mycobacterial, viral and tumour antigens [41, 42]. Conversely Th2 exhibits an anti-inflammatory profile by secreting cytokines IL-4, IL-10, IL-25, IL-9 and IL-13 [43-50]. These cytokines are necessary for guarding against extracellular microbial infiltrates which includes parasites [34, 51]. Furthermore, IL-5, IL-13, IL-4, IL-9 and IL-25 are important during allergic reactions while IL-4 and IL-10 sustain inflammatory balance by enhancing Th2 and $CD8^+$T cell differentiation and suppressing elevated pro-inflammatory immune responses respectively [43-50]. The Th17 cells noticeably produce pro-inflammatory cytokines, IL-17 (IL-17A and IL-17F), IL-22, IL-21 and TNF-α and regulate pro-inflammatory chemokines CCL2, CCL3 and CCL20 [52, 53]. The IL-17 cytokine recruits neutrophils and stimulates antimicrobial peptides, proinflammatroy cytokines and chemokines [54-57]. Similar exist between Both Th1 and Th17 may have comparable effects owing to their ability to increase the production of pro-inflammatory cytokine IFN-γ [58]. TGF-β and IL-6 are components of the Th17 differentiation complex [59, 60] and their increase will indirectly favour Th17 production. Perturbations in Th17 resulting from modifications by antigenic components can

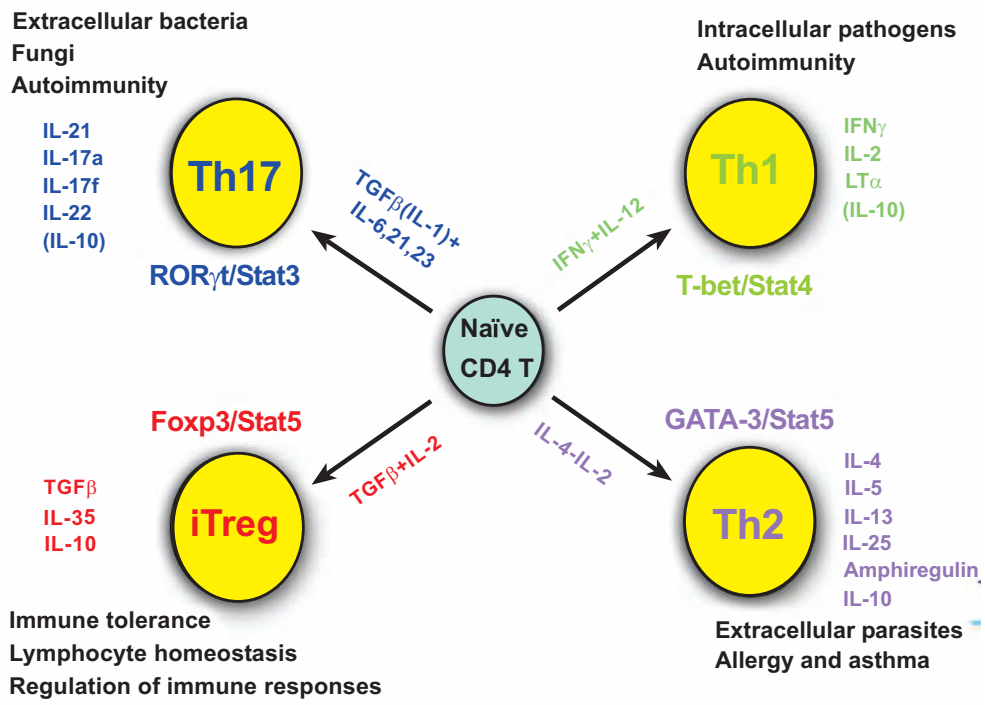

Fig. (1). Differentiation of CD4 +T cells. CD4+T cells differentiate into various subsets under the right stimulation and in the presence of the appropriate transcription factors [33].

induce systemic intestinal inflammation and anti-apoptotic molecules [61-64].

Lastly, Tregs comprise 5-10% of all $CD4^+$T lymphocytes [65]. They express the forkhead/winged helix transcription factor (foxp3) belonging to the Foxp subfamily of transcriptional regulators that suppress or activate transcriptional processes [66, 67]. Foxp3 indirectly modulates the release of pro-inflammatory factors from Th1 cells and other cells *via* the suppression of IL-2, and IFN-γ. This prevents autoreactive T lymphocytes and inflammation [68, 69]. Tregs secrete IL-10 and TGF-β [70], which is required for Th17 differentiation while IL-10 dampens pro-inflammatory responses from Th1 cells [59]. Tregs can also secrete anti-inflammatory cytokines including IL-5 and IFN-γ [71-74]. These cytokines stimulate the production of T lymphocytes, inhibit excessive proliferation of naïve T lymphocytes, regulate $CD4^+$ and $CD8^+$ T cell numbers and suppress autoimmune reactive cells [75-77], processes necessary for the maintenance and sustenance of physiological homeostasis. As AAS have anti-inflammatory properties, uncontrolled use or controlled overuse, as an ergogenic substance can be detrimental to the function of cells such as $CD4^+$T cell subtypes as these cells are necessary for maintaining immune homeostasis.

AAS Abuse

Although there is evidence to suggest that AR on T lymphocytes are inactive in the presence of androgen, these receptors may be activated by other means in the absence of androgen. The abuse of AAS may result in an influx of AAS molecules resulting in competition for available receptors or incessant ligand receptor binding interactions resulting in increases in muscle mass and strength. Anabolic androgenic steroids and their derivatives, bind to the androgen receptors at different affinities, for example trenbolone binds to androgen receptor at a much higher intensity (5x) than testosterone perhaps suggesting that it may be able to have a more pronounced effect hcompared to testosterone. Testosterone uptake at increasing concentrations can have significant observable effects which may strongly be dependent on the dosage and duration. Hence, high doses over a long period of time may induce above optimal physiological effects including physiological levels of testosterone. These changes may affect immune function as crosstalk between the immune system and androgens is necessary for homeostasis. Androgen receptors are located on skeletal muscles, thus when testosterone binds to them activating a cascade of events that induce the transcription of genes required for modulating the growth of muscle fibres. An increase in the uptake of testosterone increases recruitment and activation of androgen receptors at the surfaces of cells of the skeletal muscle. This generates an increase in muscle fibres and a boost in the presence of androgens and ligand androgen receptor interactions. This is evident in the observation that after administration of testosterone enanthate for 10-20 weeks in the absence of exercise there is an expansion in lean body mass, muscle size, and muscular strength [78]. Other effects of AAS include an increase in protein metabolism, bone metabolism and collagen synthesis [79-82].

Excessive consumption of AAS can alter conditions at the genomic level. In particular, DHT alters the expression of genes containing the androgen response element promoter regions including AKr1a1, Gstp1, Stat5a, Xrcc5 and Gsn [83]. Most of the genes that are affected as a consequence of

DHT administration are involved in both apoptosis and pro-apoptotic activities. Administration of DHT over long periods may be advantageous to lymphocytes as they have the potential to promote the survival of lymphocytes by making them more resistance to programmed cell death. This may be advantageous in the incidence of tumour growth as it may increase survival and proliferation of tumour cells [83]. Additionally DHT also influence the expression of lymphokines from T cells such as the IL-4, IL-5 and IFN-γ [14].

In murine studies, dehydroepiandrosterone (DHEA) has been shown to decrease IL-6 while increasing IL-2 secretion and NK cytotoxic activity [84-88]. It is also known to regulate the production of cytokines by lymphoid and myeloid cells specifically IL-2 from Th1 cells [84]. While DHEA enhances Th1 cytokine secretion it can also decrease Th2 cytokines in particular IL-10 and also IL-6 [89-92]. DHEA nonetheless causes decreases TNF-α and IL-1β. Hence, DHEA is more anti-inflammatory and less pro-inflammatory this may be attributed to its ability to prevent the action of the transcription factor NF-kβ [93], this transcription factor is known to be involved in the secretion of IL-6 and other cytokines. At optimal physiological concentrations DHEA can increase cytotoxicity [15], specifically, NK cytotoxicity [94].

Further, there are two forms of androstenediol (AED) α/β, and these can have either a negative or a positive effect on hematopoiesis, immune cell activation, resistance to infection and tissue damage. For example, it is well known that αAED increases apoptosis through RANKL [95]. Hence when taken at higher concentrations for recreational purposes, this can affect the life of the cell. β-AED on the other hand decreases cell death and maintains survival [96]. These separate distinct functions must be taken into consideration when considering these drugs for body enhancement. Trenbolone and stanozol are mainly used on animals, excessive use of these drugs may be harmful as they are genotoxic on lymphocytes [97]. These drugs may induce chromosomal alterations in the structure of the lymphocytes which can change events in the cell cycle and potentially be lethal or generate mutations. At supraphysiological levels, stanozolol is able to increase the concentration of cells of the liver and this may include lymphocyte subsets. Nandrolone testosterone, norandrostenedione also increase the levels of Ca^{2+}, activating endothelial receptors and a cascade of events including the release of additional Ca^{2+} from storage centres [98].

IMPLICATIONS OF AAS ABUSE ON T CELLS

Androgen receptors are present on most cells including niave T cells hence they can be excessively activated when administered at high doses. Although administration of AAS may seem to be advantageous to some extent, it may be detrimental during prolonged usage when the concept of anti-and pro-inflammatory balance are taken in to consideration. As stated above, Th cytokines regulate the inflammatory cascade. The exact role of AAS on Th cytokines shifts is not entirely known some forms of AAS may be implicated in the induction of cytokines that regulate Th cells and their cytokines. DHEA increases the production of IL-2 a key factor in the generation of Th1, Th2 and Tregs [99]. However, this maybe only beneficial for Th1 and Tregs as IL-4 which is required for Th2 generation is decreased in the presence of high amounts of DHT [100]. Nonetheless AAS may have distinct effects on the production of Th1 cells as they can either promote or block these cells by acting on IFN-γ. While testosterone prompts an increase in pro-inflammatory cascade through increase IFN-γ, DHT acts to dampen these effects. Conceivably, combination of AAS at elevated doses may offset the anti- and pro-inflammatory balance or Th1/Th2 shifts.

AED is a potent Th1 suppressor and most useful in diseases with a predominant Th1 profile such as Multiple Scelerosis and Experimental Autoimmune Encephalo-myelitis (EAE). In these diseases, AED inhibits exceeding levels of TNF-α and IL-6 in an attempt to prevent inflammation and restore inflammatory balance [101]. TNF-α acts by binding to two receptors TNF receptor (TNFR)1 and TNFR2, binding to TNFR1 produces pro-inflammatory immune related responses while TNFR2 regulates TNFR1 and Treg responses, T cell survival, priming cytotoxic T cells and assists in eliminating viruses [102, 103]. Similarly, DHEA although significantly useful in trauma and autoimmune diseases may reduces peripheral CD4+T cells and TNF-α [104]. In healthy individuals, abuse of AED and/or DHEA can therefore affect the function of TNF-α and consequently T cells.

The IL-6 cytokine, can stimulate AR-mediated transcription causing an increase in the expression of genes [105]. In the presence of testosterone and DHT, IL-6 and its receptor diminish [106] so these situations create imbalances in the CD4+T cells. IL-6 is necessary for maintaining both Th1/Th2 and Th17/Treg immune shifts, this may be necessary in ensuring immune homeostasis and prevention of auto reactive events. Importantly, IL-6 potentiates Th2 and Th17 survival thus supporting both an anti- and pro-inflammatory immune state [59, 107, 108]. A decrease in IL-6 is also suggestive of a heightened activity in Tregs. In the absence of an autoimmune disorder, targeting of IL-6 may be unfavourable to other immune components. IL-6 in conjunction with TGF-β directs Th17 survival and differentiation *via* activation of transcription factors, the orphan nuclear receptors, retinoid-related orphan receptor (ROR)γt and RORα [109]. Conversely, AAS regulation of IL-6 may serve as a protective mechanism against prostate cancer where IL-6 and its receptor are upregulated [110] although this may not be true in all cases as AAS can adversely induce prostate cancer [111].

T cell proliferation, differentiation in to various subtypes and effector function is in part controlled Ca^{2+}. Increase in intracellular Ca^{2+} activates a sequence of phosphorylation events that trigger the activation and release of transcription factors such as the nuclear factor of activated T cells (NFAT). An influx of Ca^{2+} occurs following AAS, as a consequence of over stimulation of the T cell receptor by a surge in androgens. This subsequently stimulates the phosphorylation of tyrosine based motifs, membrane associated linker of T cell activation and Src homology domains [112, 113]. These actions can potentially activate NFAT transcription resulting in an surge in T cell related

transcription factors T-bet, Gata3, RORγt and Foxp3 [114]. These transcription factors are required for the generation of subsets of the CD4+T cells. Sustained Ca^{2+} therefore produces sustained NFAT transcriptional regulatory effects on other genes hence causing an increase in cytokine and chemokines release and Treg suppression [115]. These changes may have implications on health in the long run.

Lastly, concentrations of estrogen may increase during supraphysiological doses of AAS. Estrogen increases the prevalence of Tregs and conversion of subsets of CD4+T cells into Tregs at high concentrations [116]. Most AAS users also administer aromatase inhibitors to limit the occurrence of estrogen. Aromatase inhibitors are therapeutic in various forms of breast cancer as they limit the effects of an increased population of Tregs and autoreactive Tregs [117]. However, aromatase in the absence or presence of cancer can significantly reduce bone density [118] and surface molecules necessary for Foxp3+Treg function including molecules such as cytotoxic T lymphocyte-associated 4 (CTLA-4), glucocorticoid-induced TNFR- related gene (GITR), CD25, and CD134(OX40) [119]. Although, there are no reports on Tregs and AAS abuse it is likely that both AAS and aromatase inhibitors have some effects on Tregs proliferation and function which may be detrimental to the overall immue homeostasis

CONCLUSIONS

Androgenic Anabolic Steroid abuse has substantial effects on immunocytes and immune function. Importantly, AAS abuse may result in an increase in either pro or anti-inflammatory markers or Th1 and Th2 cytokines. These changes may offset the normal immune functions and activate other mechanisms that may have adverse effects on immune function. Shifts in the dominance of the $CD4^{+}$T cell subtypes may provoke immune dysregulation that may have either systemic or autoimmune consequences. Additionally, as AAS are able to regulate gene expression changes excessive use of these drugs altering gene expression may affect other physiological processes such as cardiovascular function. Although the incidence of AAS on small molecular RNA has not been widely investigated, if AAS have the ability to modify gene expression changes and transcriptional factors they may also regulate miRNA causing either a depression or elevation of certain genes. These may not necessarily be useful for optimal physiological function. Further studies are therefore required to assess the role of these AAS on normal healthy individuals.

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Received: December 10, 2010 Revised: January 14, 2011 Accepted: February 07, 2011