Review Article

The multiple roles of steroids and anabolic steroids and its relations to cardiovascular and musculoskeletal pathology: a brief review

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Abstract

Steroids are defined as compounds included in the family of terpenoid lipids. Specifically, anabolic steroids are synthetic steroids of the androgen steroids. Since the beginning of the 20th century, anabolic steroids have proven influence on physical strength, endurance and muscle tissue synthesis. They have been used both for military purposes as well as for athletic achievements. Their use has been expended thereafter up to the point that side-effects began to become apparent. To date, it is well documented that anabolic steroids have adverse side effects on the primary and secondary sex characteristics. Steroids attribute male characteristics to females, and, at the same time, sterility and erection dysfunctions to males. Several studies have shown that the use of anabolic steroids is connected to dysfunctions of the cardiovascular system. No direct adverse effects have been reported on the function of cardiovascular system during the use of anabolic steroids, however, it has been shown that there is an indirect connection between anabolic steroids and cardiovascular disease. Steroids elevate levels of cholesterol and triglycerides which both are related to high risk of cardiovascular disease. The present work reviews the hitherto known connections between steroids in general, both synthetic and naturally occurring to the risk or not of cardiovascular disease.

Keywords: Corticosteroids, Anabolic steroids, Cardiovascular, Musculoskeletal

Introduction

A historical background

Steroids constitute a special category of compounds, which are abundant to all organisms ranging from lower species in the evolutionary chain to higher mammals and humans. A special subcategory of steroids determine sex in organisms and are produced by the gonads in humans. Naturally occurring steroids and synthetic steroids are utilized for treatment purposes or as anabolics. Flashing back to the history of anabolics, it is worth mentioning that the action of steroids as artificial strengtheners is known since the early 1930s. At that time, testosterone was found to be the hormone that attributes the sex characteristics to males and participates in sexual maturation of juveniles. Further on, tests of steroids as medication alternatives were reported back in the late 1930s. They were used in cases known as “the Eunuch syndrome”, sexual impotence, starvation, crypsorchy and through treatments, in cases of extended burnings¹. Until

then, however, they were known only for their therapeutic applications. At the same time, steroids became popular for their anabolic characteristics. In particular, it became evident that steroids were contributing to the formation of muscle tissue and improvement of physical endurance. Such experiments were performed for the first time in Nazi Germany in the late 1930s (approximately 1939) and came to certify that steroids did have an impact on muscle formation and endurance². Thereon, steroids have

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become popular for their anabolic effect. In addition, they have been used extensively to the treatment of prisoners of war who have suffered severe long-term starvation and multiple injuries³. This was just the beginning. During the Olympic Games, through the period of 1954 to 1972, the use of anabolics among athletes exceeded 70%. Remarkable is that on November 25th 2008, an article in “*The New York Times*” referred to the fact that athletes coming from the former East Germany had won ten out of fourteen gold medals hitting at the same time eight world records in backstroke at the 1973 Olympics. Later on, those gold medals were discovered to be won due to the use of anabolics instead of intensive workout. Likewise, most noticeable is the fact, revealed after the unification of Germany that Eastern countries, under the Russian sphere of influence, had been sending female athletes to the Olympic Games in their fourth month of pregnancy. This used to happen because the hormonal balance of pregnancy, included steroid hormones, attributed extensive muscle and joint flexibility to the athletes as well as physical endurance and therefore, better performances. The use of steroids in athletic events had been epidemically increasing and as a result they were banned at the Olympics of 1976 and thereafter⁴⁻⁶. Today, the use of steroid anabolics is restricted to therapeutic methods only and the supplement use for sportive purposes is prohibited. However, statistical data from the United States of America point out another dimension of the issue called steroids as anabolics. Until 1989, 11% of teenagers had stated steroid use, of whom 65% were tempted by performance- enhancing reasons and the other 35% by cosmetic reasons^{7,8}. The percentage of 11% increased in the late 1990s approaching that of 20%, indicating the alarming fact that the proportion of users among adolescents and juveniles was on the rise every year. The use of anabolic steroids in Greece seems to be kept at lower levels compared to international data, yet with an increasing trend. In particular, it has been found that in a sample population of 2000 juveniles, 2% declared usage of anabolic steroids of whom 1.2% were males and 0.8% females.

Molecular structure, taxonomy and function of anabolic steroids

Steroids are compounds that belong to the greater family of *terpenoid lipids*. These are characterized by the typical carbon-four ring structure. The precursor molecule of steroids is *Acetyl-CoA*, which is the precursor of *dimethylallyl pyrophosphate (DMAPP)* and *isopentenyl pyrophosphate (IPP)*⁹. The end product of these is *lanosterol* which constitutes the first steroid to be formed and from which the rest steroids occur. Another metabolic pathway, from which several steroids result is the *cholesterol* pathway. The process is called *steroidogenesis*, due to the fact that new steroids derive from the already preexisting ones.

Androgens are products of *cholesterol*. As mentioned above, androgens (to which we shall refer in detail further on), belong to the family of compounds known as *sex steroids* including androgens: *testosterone*, *androstenodione*, *dihydrotestosterone*, *anabolic* steroids and estrogens: *estradiol*, *estrone* and the progestones; *progesterone* and *progestines*.

Sex steroids have the utmost significant role in the organism development in general, concerning not only humans but also other inferior organisms in the evolutionary chain. Therefore, they participate in the formation of what it is called *primary* and *secondary* sex characteristics. These include among others, development of facial hair in males, tone of voice in both sexes and maturation of reproductive organs such as the *epididymis* in males and *endometrium* and *clitoris* in females. Lack or dysfunction of those steroids leads to severe dysfunctions of the organism as a whole or to several syndromes like the *Klinefelter syndrome*, where a *XXY trisomy* leads to *gynecomastia* and under-developed testicles. Consequently, this effect induces gonads dysfunction leading to reduced testosterone production.

Anabolic steroids are synthetic products of androgen steroids and mainly that of testosterone. In order to simulate or even enhance the efficacy of synthetic testosterone, anabolic steroids are being manipulated. So, esterification of 17- β -hydroxy group, alkylation of the 17- α -carbon atom and finally modifications on the cyclic hydrocarbon chain comprise the steroid structure². Indicatively we refer to some of the most popular and known anabolic steroids: *Nandrolone*, *Stanozole*, *Boldenone*, *Androstenedione*, *Androstenediol*, *19-Norandrostenedione*, *19-Norandrostenediol*, and *DHEA* (*Di-hydro-epiandrosterone*), (β_2 -Agonists): *Clenbuterole*, *Formoterole*, *Salvutamol*, *Salmeterole*, *Tervutaline* and so on.

The intake of anabolic steroids can be separated into two main categories: pharmaceutical i.e. use as medication and anabolic uses. Anabolic steroids have to utilize two pathways of action: First of all, they stimulate protein synthesis and second, they are antagonists of the naturally occurring steroids cortisol, which participates to the mechanisms involving reactions to stress¹⁰. Therefore, they promote cell proliferation and growth and in particular muscle tissue and bone. It has been reported that they function as antagonists of another category of steroids, the glucocorticoids (GCs), which participate in exactly the opposite mechanisms, i.e. they are factors of response to stress factors in such a way that they induce muscle tissue catabolism and bone as well^{11,12}. This difference is accomplished through the stimulation and activation of different intracellular receptors. These receptors belong to the super-family of nuclear receptors known as steroid receptors. For example, the androgen receptor (AR) consists of three functional domains: the *N-terminal* domain, the *DNA-binding* domain (DBD) and the *Ligand Binding Domain* (LBD) the part where the actual ligand, the androgens, are linked. In general, the AR functions are based mostly on the binding of the ligand on

Figure 1. The Androgen receptor and its binding with testosterone. The ligand (testosterone) appears in white while the domains of the receptor protein appear in red and green. (Source: <https://www.ncbi.nlm.nih.gov/Structure/pdb/2AM9>, PDB ID: 2AM9: Crystal Structure of Human Androgen Receptor Ligand Binding Domain in Complex with Testosterone)⁶³.

the receptor and further on, passing into the nucleus. These receptors function not as monomers but as dimers, which dimerize after ligand binding (Figure 1). As a result, after its passing into the nucleus, it functions as a transcription factor, which is one of the most important functions of this family of receptors. It regulates genes that are responsible for cell proliferation and cell growth, among others, since it is known that steroid receptors regulate almost half the genome. The functions of anabolic steroids, as well as of others, depend mainly on the binding affinity of the steroid to its respective receptor^{13,14}. For example, the steroid *methandrostenolone* does have a low binding affinity to the AR receptor and promotes mainly the synthesis of proteins and glycolysis¹⁵. As opposed to that, the steroid *oxandrolone* does have a higher binding affinity on the AR receptor and consists of a promoter of transcriptional activity. Another example, recently known from the Greek Olympics team in the Olympic Games of Beijing, is *methyltrienolone* (M3). It is an anabolic steroid with extremely high binding affinity to the AR^{16,17}. In fact, it is so effective that it is used as a marker for the detection of the AR in cases of prostate or urinary bladder cancers. From a pharmacodynamic point of view, steroids possess a special characteristic to which their action is attributed: It is the property of entering the cell membrane passively into the cytoplasm without the need of membrane receptor.

Administration of anabolic steroids is applied through three main paths, orally, intra-intestinally and over the skin. The administration of steroids orally has been considered as a risk factor for hepatic cancers¹⁸.

Uses and side-effects of anabolic steroids

Anabolic steroids are used for therapeutic reasons and secondarily for cosmetic reasons. Pharmacological use is indicated in cases of anorexia, development of the bones and muscle tissue, for example, in anorexic and osteoporotic individuals. Such a steroid used for these indications is the 19-nortestosterone (trade name *Deca durabolin*). It is administrated in cases where muscle and bone reconstitution are essential and if not adjusted will be life-threatening especially in elders, anorexic individuals, in cases of severe burnings and so on. The uses of steroids for cosmetic reasons include increase of muscle tissue, fast muscle built-up, restriction of adipose tissue and so on.

In cases where anabolics are given in the framework of a treatment, they have minor side-effects since they substitute a missing or dysfunctional area of the homeostasis of the body. On the other hand, there is a big debate on the side effects of steroids when used for cosmetic reasons. Their use does not discriminate between the sexes since it appears that both sexes use steroids and, in cases, extensively. The main reason is the improvement of athletic performance and endurance. In males, long-term use of anabolics causes oligospermia, gynecomastia and impotency. At the same time, as aforementioned, it is considered to be a risk factor for hepatic cancer. In females, it appears that it manifests exactly the opposite effects. In other words, it induces the appearance of masculine characteristics such as deepening voice, increase of hair in the areas controlled by AR such as the area of the genitalia and face.

Furthermore, long-term uses of the anabolic steroids, both for pharmacological or cosmetic purposes revealed a series

Figure 2. Distribution of anabolic uses and reasons. (Source: Figure reproduced from data from Korkia & Stimson 1997)¹⁹.

Figure 3. Death Distribution caused by cardiovascular diseases. (Figure reproduced from data from the American Heart Association/CDC/NCHS).

of side-effects concerning the cardiovascular systems. The main uses of anabolic steroids are presented in Figure 2¹⁹.

The effects of anabolic steroids on the cardiovascular system

It has been reported that the side-effects on the cardiovascular system are dose-dependent and probably time-dependent as well. That means, the larger the doses and the longer the time interval administered, the more intense the effects on the cardiovascular system are. Unfortunately, these side-effects do not discriminate

between pharmacological and cosmetic uses.

Those effects can be divided in two categories: the direct and indirect side-effects. The indirect ones appear when the influence in the cardiovascular system is on secondary physiological mechanisms such as blood pressure, which increase due to the use of anabolic steroids²⁰. In addition, it has been reported that the use of anabolics increases the levels of *LDL* and decreases those of *HDL*²¹, which develop, as a secondary side-effect, the increase of blood pressure and the apparition of cardiac dysfunction due to the effect of atherosclerosis²².

Figure 4. Distribution of anabolic steroids used as found from a population of positive samples. (Figure reproduced from data from the American Heart Association/CDC/NCHS).

Moreover, it has been reported that anabolics afflict the levels of glucose tolerance which makes them indirectly responsible for metabolic syndromes. Therefore, it is well documented that their use causes indirectly both cardiac and coronary diseases. The next category is the direct anabolic effect which includes both anabolic steroids as well as testosterone^{23,24}.

By definition, cardiovascular diseases and all their forms (Figure 3), constitute the main cause of death in the developed world²⁵. Despite the extensive debate on the uses of anabolics and their side-effects, it is still controversial whether there is a significant causality of cardiovascular disease that can be attributed to them²⁵. Studied phenomena such as strokes, heart attacks, arrhythmias and pulmonary diseases have been impossible so far, to ascribe them to the use of anabolics compared to groups of individuals with no steroid treatment. A finding of great interest was discussed in the former Eastern Germany reporting the long-term use of anabolics on more than 2000 athletes, where after extensive examinations of their cardiovascular system, no influence or differentiation had been observed regarding the use of anabolics (Figure 4)²⁵.

Equivalently, in a case study performed on 2.418 *transsexuals* who have gone through a laborious sex-change operation from female to male and have been treated with testosterone for long periods of time no significant increase in cardiovascular diseases have been observed compared to the general population. Even more notable is an “experiment” conducted during the 1518 AD to 1858 AD years. Through that period, a tendency of puberty castration was spreading rapidly, aiming the maintenance and probably the quality of the voice on the highest octaves for artistic or even

ecclesiastical and gospel purposes (*castrati*). In other words, individuals who had gone through the process of castration were forced into a life literally without any production of androgens. Nieschlag et al. have studied the life spans of those individuals and found that no significant difference was observed as compared to the general population life span (*castrati*: 66±2 years, rest of the population: 64±2 years)²⁶. Taking into account the contribution of steroids to the overall survival of the population, it would be likely that males with sufficient and constant production of testosterone would have a lower life expectancy as to the *castrati*, since the existence of testosterone renders males more vulnerable to cardiovascular diseases.

Despite the numerous controversies concerning the uses of anabolic steroids, their presence still abides therein, especially in sports. Hence, so far, there is no concise opinion formed on the effects of anabolic steroids in the cardiovascular system. However, an opposing view has been reported where defects in testosterone production can cause *LDL* increase and *HDL* decrease and consequently atherosclerosis²⁷.

As previously stated, the extensive use of anabolics by heavy weightlifters leads to changes in the morphology of the cardiac muscle, for instance, expansion of the left ventricle and thickening of the cardiac musculature. Yet, the etiology has been attributed to the overuse of anabolics, since they reach 1000 doses higher than those of pharmacological use². In the same study, the use of anabolics are presented to be culpable for ischemic myocardium and combined with the increased lipidemic profile, although reversible, it can triple the risk of cardiovascular disease^{2,28}.

The effects of anabolic steroids on the musculoskeletal system

The musculoskeletal effects of corticosteroids frequently depend on the high or low dose treatment followed. Concerning high doses, myopathy and aseptic osteonecrosis seem to wield great influence yet not predictable, while osteoporosis and growth suppression refer to low dose therapy and more common incidental phenomena. However, the knowledge on a threshold dose defining the adverse effects is still limited due to the great amount of diseases covered and the combination of drug therapies required²⁹.

Glucocorticoid treatment is mostly responsible for secondary osteoporosis. The main effects are related to bone metabolism and concern apoptosis in osteoblasts and osteocytes with direct impact on bone formation or not necessarily well intentioned amplification of osteoblast properties. Secondary osteoporosis usually originates from chronic ailments and endangerment, while primary osteoporosis occurs due to the pathological condition of low bone mass³⁰. One fifth of all cases of osteoporosis are attributed to the use of glucocorticoids³¹.

Glucocorticoids impede stem cell differentiation in osteoblasts and affect metabolic activity by hindering new bone formation³². The glucocorticoid exposure discomposes the osteoblast- osteoclast collaboration and hence, the osteoclast apoptosis³³. Bone metabolism counts on sex steroids as well. Fractures can be led by free androgen and estradiol levels in men³⁴ and by postmenopausal osteoporosis in women. The steroid effects in this case could be meliorated by calcium and vitamin D supplementation as well as moderate exercise³⁵.

Low dose treatment involves linear growth mainly in pediatric asthmatic cases. Corticosteroids can inhibit mechanisms and organ responsiveness therefore the use of recombinant growth hormones could rehabilitate growth velocity³⁶.

Furthermore, steroid myopathy is eventuated by high dose corticosteroid treatment combined with sedentary lifestyle. Aerobic exercise can result in the prevention of this condition and particularly lead to reduction of glucocorticoid receptors on skeletal muscle cells³⁷.

Osteonecrosis is another severe yet rare side effect of high dose treatment and can lead to critical and irreversible conditions. Differential diagnosis often includes osteoarthritis, fracture and low grade osteomyelitis. The necrosis of the bone can be detected by MRI (magnetic resonance imaging) and could be interpreted as the inactivity of blood flow in the affected bone with ensuing ischemia. Early diagnosis could be proven recuperative for children still, adults are likely to undergo surgery and joint replacement³⁸.

Regarding anabolic steroids, when high doses are provided, combined with intensive physical exercise, the muscle mass is augmented due to increase of the androgen receptors on the muscle. Those androgen receptors are fewer in the lower part of the body. Androgens affect the

osteoblast- osteoclast balance and bone formation. On the other hand, tendons do not increase and therefore present rupture vulnerability, especially in adolescence. Anabolic steroid users may confront rhabdomyolysis or acute muscle or skeletal destruction as well as heart, muscle and liver enzyme dysfunctions which make medical attention a matter of necessity³⁹.

The molecular basis of anabolic steroid action

Examining the effects of anabolics, it is known that the cardiac musculature possesses three steroid receptors; the **GR** (Glucocorticoid Receptor), **AR** (Androgen Receptor) and **MR** (Mineralocorticoid Receptor).

It has been reported that aldosterone or cortisol are increased in individuals with hypertension disease, hormones which activate the MR. As a result, oxidative stress, inflammation and fibrosis occur⁴⁰. It is also very interesting the fact that lack or dysfunction of the sex hormones results in deregulation of the mechanisms of blood clotting where, on the contrary, the use of anabolics leads the mechanism of blood clotting towards the opposite direction meaning increased blood clotting machinery⁴¹. If we could categorize the actions of steroids we could discriminate two categories: the genomic and the non-genomic actions. The first category requires the binding of the steroid on its respective receptor, which is the most time-consuming process of both actions. On the contrary, the non-genomic action takes place within seconds. This could lead us to the conclusion that the effects of anabolics follow the genomic type of action since their effects have a long-term character. Interestingly, it has been recently reported that the molecular basis of cardiac arrhythmias relies mainly on the non-genomic effects of steroids as the last affect the ion pumps of the cardiac muscle⁴². An enlargement of mitochondria in the myocardium on the cellular level has been also observed. In addition to that, mitochondria become spherical shaped and the sarcomeres are being destroyed. Furthermore, testosterone is considered to be a selective inhibitor of noradrenaline in non-neuronal tissue. This property, combined with the use of anabolics and extensive exercise, caused the deformation or dissemblance of neurons of the myocardial sympathetic system in mice^{2,28}. Finally, as mentioned before, a very significant side-effect of anabolic use refers to the hypertrophy of the cardiac muscle. It has been noticed that androgens and glucocorticoids have opposing functions in the skeletal muscle. The two receptors i.e. the AR and the GR function as mutual inhibitors. Exception to this rule is the myocardium where both receptors when stimulated take an active anabolic role. In the case of a hypertrophic skeletal muscle, AR possesses a higher binding affinity for anabolic steroids. On the contrary, this is not the case in the myocardium. This does not unilaterally explain the action of androgens on that muscle and there again suggests the existence of an alternative action pathway of myocardial regulation². Hence, a major question arises since all of the

above reports have based their findings on animal models rather than human subjects. At the same time, side-effects of steroids have been attributed to overdoses administered to athletes and not steroid nature *per se*. On the other hand, efforts are being made to design *Selective Androgen Receptor Modulators (SARM)* in order to improve physical function and bone health without the side-effects accompanied by the typical steroid administration⁴³. Despite the fact that side-effects of anabolic steroids are well documented, it has not been made possible to correlate cardiovascular disease with anabolic steroids use. Unfortunately, until today, the use of anabolics is considered to be a major issue, of an increasing tendency, especially among athletes due to excessive demands for high performances and record levels.

Anabolic steroids and childhood

Being aware of the steroid effects on adult health, it is highly important to understand the effects on children's health as well. Anabolic steroids promise strong results to younger athletes who wish to boost their muscular strength and speed, in order to deliver and deal with high demands in sports or assure their positioning in professional leagues⁴⁴.

However, there is little proof of such benefits and the harm, especially on developing children, seems to exceed since anabolic steroids increase the levels of testosterone in the blood and have negative impacts on health over time. Such disorders concern stunted growth, among adolescents, where bone maturation becomes fast and then stops at an early age⁴⁵, liver tumors, several conditions regarding sex characteristics, disorders of the reproductive system, and finally, abnormal enlargement of the heart muscles and blood lipid abnormalities which lead to cardiovascular ailments⁴⁶.

The overuse of steroids is revealed overwhelmingly by volatility, acne, rapid muscle augmentation and, additionally, male- type hair growth, deepening of the voice and enlargement of the clitoris in teen girls and young women⁴⁷.

It is strongly recommended that children fully understand the concept of using anabolic steroids which involves health risk, the possibility of legal trouble and the feeling of fraud and responsibility on the whole.

Corticosteroids and childhood

Corticosteroids are used for pharmaceutical purposes only to manage inflammatory and autoimmune disorders such as asthma, allergies⁴⁸, lupus⁴⁹, Crohn's disease⁵⁰, atopic eczema⁵¹ and others. It seems that children are highly sensitive to side effects, especially the ones of growth, immunity and adrenal insufficiency therefore the intake of corticosteroids should be thoroughly monitored mostly in long-term use.

As mentioned above, corticosteroids include glucocorticoids and mineralocorticoids, used for metabolic or inflammatory cases and fluid retention respectively. Several adverse effects can appear during short or long-term treatments impinging the balance of a child's organism

in a physical or mental way⁵².

Cardiovascular complications refer to ion excretion, heart micro- vascular permeability and cardiac output as a whole. Corticosteroid chronic treatments induce increased appetite, weight gain, hypertension, and redistribution of fat, endomorphic habitus with Cushing syndrome's characteristics⁵³ and most rarely, uncontrolled blood sugar led to reversible diabetes^{54,55}.

Moreover, corticosteroids stimulate gluconeogenesis and act, by extension, upon protein and lipid metabolism which directly affect capillaries, *inter alia*⁵⁶.

On the other hand, *Addison's disease*⁵⁷, which refers to primary adrenal insufficiency⁵⁸ (cortisol and aldosterone) followed by abdominal pain and weight loss, requires long-term steroid treatment with numerous risks as well. As known, cortisol provides blood vessel, heart and blood pressure maintenance in addition to regulation of metabolism. The dysfunction of the adrenal glands may result from an autoimmune condition or a chronic use of corticosteroids which stalls natural corticosteroids to be made. Possible disorders include sensitivity to insulin, high blood levels of potassium and low blood pressure. Corticosteroids should be forthwith dispensed since it is a life- term condition and could lead to severe complications⁵⁹.

Additionally, children with congenital adrenal hyperplasia (CAH) appear to suffer from impaired longitudinal growth which needs supplementary treatment, along with glucocorticoids. Therapy is provided to children older of age since prednisolone and dexamethasone have adverse effects on infants⁶⁰.

After all, the controversy whether steroids are efficient, although commonly used, still remains.

Steroids in childhood cancer treatment

Cortisol, a forenamed hormone responsible for corticosteroids, can be encountered in synthetic versions as well, including cortisone, hydrocortisone, prednisone, methylprednisolone and dexamethasone, which, in total, are prescribed to ease the consequences of chemotherapy and radiation⁶¹.

Regardless the side- effects aforementioned, they usually reduce nausea, contribute to the alleviation of pain and headaches over brain tumors, render assistance to the fight against cancer cells and reduce allergic reactions⁶². Nevertheless, due to the severe side effects, patients, guardians and physicians should act in full consultation for the best possible outcome.

Conclusions

Corticosteroids and anabolics are known to have a variety of effects on a plethora of physiological systems. These effects are well documented, yet the exact mechanisms still remain to be elucidated. In the present work we have reviewed the present knowledge on the effects of anabolics on the cardiovascular and

musculoskeletal systems. It is well known that although short-term effects are beneficial for the receiving party, long-term effects have been found to be malicious, with a great range of side-effects. The controversial nature of steroids, is mainly attributed to the dual character of the respective receptors, which control gene regulation.

Authors' contributions

MT: collected literature, drafted the manuscript. **AN:** collected literature, drafted the manuscript, **GIL:** drafted the manuscript, proof-read the manuscript, provided critical review, gave final permission for submission. All authors read and approved the final manuscript.

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