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The effect of ergogenic substances on liver function in athletes – a literature review

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ABSTRACT

Introduction

Athletes commonly use ergogenic substances, ranging from natural to pharmacological agents, aiming to enhance their performance. This review analyses their risks in terms of hepatotoxicity and liver health.

Materials and Methods

A thorough research was conducted using the following databases: Embase, PubMed, Cochrane Library, and Google Scholar, in accordance with PRISMA guidelines. The keyword choice was decided based on the subject of the review beforehand.

The Stage of Knowledge

The review subsumes anabolic-androgenic steroids (AAS), selective androgen receptor modulators (SARMs), creatine, caffeine and herbal supplements. Despite strict bans, AAS and SARMs are widely abused, also among youth. Many of them display serious adverse effects, including consecutive signs of liver damage culminating in drug-induced liver injury (DILI). Moreover, SARMs present severe testosterone suppression.

Overall, the safety profile of exogenous creatine is good and non-hepatoxic. The reports of serious side effects remain anecdotal. Additionally, there is a rising number of reports on the therapeutic application of creatine, also in terms of the liver.

Caffeine effectively enhances endurance and glycogen recovery. Green tea, rich in catechins, minimises exercise induced muscle-damage and, by lowering AST levels and reducing oxidative stress, actively protects the liver. Both maintain a favourable safety profile.

Summary

Ultimately, the impact of ergogenic substances on liver health ranges from highly toxic to safe, even beneficial, within a broad spectrum. This contrast highlights the critical need for athletes to consider the severe adverse effects of any illicit and harmful substances against those proven to be both safe and effective. It is all in terms of their own well-being and the trends that later spread among people they are being looked up to.

Key words: ergogenic aids, hepatotoxicity, athletes, liver health, creatine monohydrate

1. Introduction

Nowadays, the use of performance-enhancing substances among athletes is a widespread phenomenon (1, 2). Studies have shown that ergogenic substances such as protein or creatine, through their ability to improve short-term performance, enhance sprinting, agility and, in women, jumping performance as well (1, 2, 3). Plant-based supplements also play a significant role here, an example being beetroot juice, which contains nitrates that improve oxygen delivery to the muscles (3). The use of pharmacological agents such as painkillers or AAS is also very common in sport (1, 4). The former, in addition to their therapeutic use, were sometimes intended to improve training performance or prevent a decline in athletic form (4). The latter are used to rapidly increase muscle mass and, despite a widespread ban on their use for sporting purposes, are still frequently used (5).

Some of the above substances have a significant negative impact on liver function (9, 13, 15), which in turn plays a key role in regulating blood sugar levels, detoxification, protein synthesis and drug metabolism (6).

This review aims to analyse the risk of hepatotoxicity depending on the type and dose of the agents used.

2.1 Anabolic-androgenic steroids – prevalence of use, hepatic metabolism and hepatotoxicity

AAS are endogenous compounds and are primarily responsible for the induction and maintenance of secondary male sexual characteristics and muscle growth (5). Despite a widespread ban on the use of these substances in sport, they remain popular among athletes due to their easy availability via the internet or local dealers (5, 7). Based on an analysis of 187 studies, it was calculated that 3.3% of participants had used steroids, with men being four times more likely to do so than women (8). Another study shows that 14% of young athletes and 30–75% of professional athletes and bodybuilders use AAS (9).

Androgens can be administered in the form of transdermal testosterone gel or patches, but their half-life is short. To prolong their action, testosterone esters in the 17-hydroxy group are used, administered intravenously in oil (5, 7). This makes them less hydrophilic and more lipophilic (5). We also distinguish 19-nortestosterone and derivatives with greater anabolic than virilising effects (7). The third type consists of compounds alkylated at the C-17 position, which are characterised by the fact that they are administered orally (7). Absorbed AAS reach the liver

via the portal vein, and compounds that have not been previously modified are largely metabolised by the liver, resulting in a high first-pass effect (5, 10). After absorption into the bloodstream, 1% to 4% circulates in an unbound form, whilst the majority of AAS binds to corticosteroid-binding globulin (CBG) and sex hormone-binding globulin (SHBG) (7). AAS pass from the bloodstream into the extravascular space, from where they diffuse directly into the target cells (5).

After crossing the cell membrane, they may bind to the androgen receptor (AR) to elicit a specific biological effect, or undergo biotransformation. This metabolism can occur in three ways: by converting the compound into a stronger androgen, into a form with weaker activity (or completely inactive), or into oestrogens (5). In the liver, among other places, testosterone is bioactivated into a stronger androgen – dihydrotestosterone – but despite its activity, it has little effect on muscle growth (11). The liver regulates the activity and clearance of hormones through a two-phase metabolism. Phase 1 is responsible for the reduction of Δ4 bonds and 3-keto groups, oxidation by P450 enzymes, and dehydrogenase (HSD) reactions at the 11-β and 17-β positions. These processes alter the structure of androgens, preparing them for final inactivation (12).

The hepatotoxicity of SAA is a complex process, the severity of which depends primarily on the type of substance, the dose and the duration of exposure (7, 13). Alkylated compounds pose a particular risk to the liver parenchyma (5, 7); because they are cleared from the liver more slowly, they become more hepatotoxic (13). This may manifest as elevated liver transaminase levels, acute cholestatic syndrome, chronic vascular damage or fatty liver, leading to liver failure (7, 13). Furthermore, patients may experience internal bleeding, the development of hyperplasia and cholestasis, which in laboratory tests manifests as increased bilirubin levels and alkaline phosphatase activity (7). It is worth noting that many of these adverse changes are reversible and may resolve upon discontinuation of administration (7). Both testosterone and dihydrotestosterone increase lipogenesis in human hepatocytes from female (but not male) donors, and androgens play a key role in the development of hepatocellular carcinoma (12). It is also believed that the activation of androgen receptors in the liver causes an increase in reactive oxygen species, leading to mitochondrial degeneration, which in turn results in the clinical symptoms of AAS-induced hepatotoxicity (14). It is worth noting, however, that certain liver markers such as ALT, AST and LDH may remain elevated for up to 7 days following intense physical exertion (15). For this reason, tests should be carried out at least 1 week after exercise. In contrast, GGT and bilirubin levels do not appear to rise as a result of physical exertion (16). When assessing liver function, individual liver markers should therefore be

compared together, as an elevation in cholestatic markers, even following recent exercise, is a strong indication of liver damage (16).

2.2 The Rise and Risks of Selective Androgen Receptor Modulators (SARMs)

Selective androgen receptor modulators (SARMs) represent a novel class of therapeutic compounds designed to exert direct, tissue-selective anabolic effects on skeletal muscle and bone. The conceptual foundation of SARMs originating in the late 1990s with pioneering work by researchers such as James T. Dalton aimed to isolate the muscle-building properties of androgens from their systemic side effects. Dalton and his team were instrumental in the early development of Andarine (S-4) and Ostarine (MK-2866) (17), which exhibits a strong binding affinity for androgen receptors..

The first non-steroidal compounds to demonstrate true selective agonism of the androgen receptor were developed by Ligand Pharmaceuticals in the early 2000s. A prominent example is Ligandrol (LGD-4033), which mimics the transcriptional effects of dihydrotestosterone (DHT) at the androgen receptor but exhibits high tissue selectivity (18). The primary clinical promise of these drugs was the ability to selectively stimulate muscle and bone tissue growth, resulting in increased muscle mass and strength. In comparison to traditional anabolic-androgenic steroids (AAS), the potential systemic side effects which include prostate hypertrophy, virilization in females, severe cardiovascular complications, gynecomastia, and male pattern baldness were theoretically expected to be diminished due to this localized selectivity (19).

These novel therapeutics offered significant promise for treating patients suffering from muscle-wasting conditions (cachexia), sarcopenia, and osteoporosis. However, owing to their potent anabolic properties and ability to enhance strength, SARMs quickly became subject to widespread abuse by athletes, bodybuilders, and fitness enthusiasts seeking expedited physical results. Consequently, a prominent illicit online market has emerged, with many of these unapproved compounds being manufactured in overseas laboratories and sold with highly questionable purity.

The prevalence of SARM abuse among young demographics is particularly alarming. It is estimated that around 1% of high school teenagers have admitted to abusing performance-enhancing substances, including SARMs and traditional AAS (20). A notable survey focusing on the social media platform Reddit, which is widely utilized by young demographics, revealed striking statistics regarding illicit acquisition and medical oversight. The study found that 90.1% of users purchased SARMs online, and a staggering 93.2% did not consult or inform

their physician about their usage. Regarding the specific compounds utilized, Ligandrol (LGD-4033) was the most popular at 56.0%, followed closely by Ostarine (MK-2866) at 53.9%, and Testolone (RAD-140) at 41.1%, with many young users admitting to "stacking" or using multiple types simultaneously (21). This data underscores the prominence of these experimental drugs among the youth. Furthermore, while general population usage remains lower, the prevalence among dedicated recreational athletes has been reported to be as high as 3% (22), demonstrating the deep entrenchment of selective androgen receptor modulators in modern fitness culture.

Despite the initial hypothesis that SARMs would circumvent the adverse effects associated with traditional steroids, the reality of their side effect profile is highly concerning. The aforementioned Reddit survey indicated that almost one in three users complained of noticeable side effects. The most frequently reported issues included mood swings, decreased testicular size, and acne (21). Other significant adverse effects include profound suppression of endogenous testosterone, insulin resistance, severe lipid profile alterations and cardiovascular strain (23).

Perhaps the most alarming medical concern is the growing evidence of hepatotoxicity, which can escalate to life-threatening liver failure. When SARMs were first synthesized, researchers hoped they would avoid the liver toxicity notoriously associated with traditional steroidal anabolics. However, numerous recent clinical case reports demonstrate that SARM use can induce severe drug-induced liver injury (DILI) (24,25,26,27). Currently, the prevailing biomechanical hypothesis used to explain this hepatotoxicity is that the molecular structure of certain non-steroidal SARMs exerts hepatic stress and requires liver metabolism pathways that closely mimic the hepatotoxic properties of 17α-alkylated AAS (28).

2.3 Creatine - role, mechanism and safety profile

Creatine, or β-methylguanidinoacetic acid (C4H9N3O2), is a glycine derivative with a methyl and amidino group, linked to a nitrogen atom. In the body, it is synthesised by the kidneys, liver, pancreas, adipocytes, and skeletal muscle from L-arginine, glycine, and L-methionine using the enzyme guanidinoacetate methyltransferase (GAMT). Later, it is distributed primarily to skeletal muscle, the heart, and the brain (29,30,31). The creatine transporter protein (CRT or SLC6A8) is responsible for its distribution (31). It is stored primarily as a phosphate, phosphocreatine. Exogenous creatine supplementation is useful during anaerobic exercise and may have neuroprotective and cardioprotective effects (29,30).

In tissues, the enzyme creatine kinase (CKM) catalyses the binding of a phosphoryl group to creatine to form phosphocreatine. Phosphocreatine transfers the resulting phosphate moiety to adenosine diphosphate (ADP) to regenerate triphosphate (ATP). It acts as an important energy storage mechanism of cells, localised in sites of high energy production and consumption (29,30,31).

CKM exists in four isoforms, each encoded by a distinct gene (30,31):

- cytosolic
  - CKM (muscle-type)
  - CKB (brain-type)
- mitochondrial
  - CKMT1 (ubiquitous-type)
  - CKMT2 (sarcomeric-type)

As a naturally occurring molecule, 2 g of creatine is ingested per pound of fish or meat, which is a daily total requirement for a 70 kg male body (32,33). Yet, the mainstream purpose as an ergogenic substance began with the 1992 Summer Olympics in Barcelona (32). As of today, it is available in the form of creatine monohydrate (29). The creatine loading protocol consists of 15–20 mg/day divided into 3 to 4 doses for a minimum of 5 days (34). It has been mostly associated with increased power output during resistance exercise and increased muscle glycogen stores when combined with the consumption of high carbohydrate diet.

Universally, creatine supplementation is safe for the athelets and has several health benefits (35,36,37). Besides enhancing acute exercise capacity and increasing muscle mass, creatine may help in managing blood lipid levels (lower cholesterol and triglycerides), decrease homocysteine, act as an antioxidant, and support glycemic control (35). Moreover, there have been reports of therapeutic efficacy in osteoarthritis and fibromyalgia, depressive states, as well as enhancing cognitive function in older populations (35). Creatine may support the treatment of sarcopenia in chronic liver disease (38). The ergogenic usage of creatine may nonetheless cause water retention. There had also been a few reports of adverse effects like muscle cramps, gastrointestinal distress, including kidney impairment and liver dysfunction. Still, the results remain anecdotal or statistically insignificant (39,40).

2.4 The use of herbal supplements and caffeine in sports and liver function

The use of herbs as ergogenic aids in exercise and sport is not novel. Ginseng, caffeine, ma huang, ephedrine and a combination of both caffeine and ephedrine are the most popular herbs used in exercise and sports. It is believed that these herbs have an ergogenic effect and thus

help to improve physical performance (41). The use of herbal medicinal products and supplements has increased during last decades. At present, some herbs are used to enhance muscle strength and body mass. Emergent evidence suggests that the health benefits from plants are attributed to their bioactive compounds such as Polyphenols, Terpenoids, and Alkaloids which have several physiological effects on the human body (42). The true prevalence of herbal product use and incidence of herbal hepatotoxicity are unknown. Unlike modern prescription medications, current regulations for herbal products do not mandate systematic surveillance or reporting of adverse events by the manufacturer to the FDA (43).

The health benefits of green tea (GT) for a wide variety of ailments, including different types of cancer, heart disease, and liver disease, were reported. Many of these beneficial effects of green tea are related to its catechin, particularly (-)-epigallocatechin-3-gallate, content. Long-term consumption of tea catechins could be beneficial against high-fat diet-induced obesity and type II diabetes and could reduce the risk of coronary disease (44). Green tea supplementation has been advocated as a strategy to improve exercise recovery due to the activity of its catechins with high antioxidant and anti-inflammatory potential. Green tea extract supplementation before an event of cumulative fatigue minimizes muscle damage and oxidative stress in trained athletes. It also shows positive effects on neuromuscular parameters related to muscle activation and muscle fatigue (45). Green tea reduced the postexercise concentration of LH and increased the values of total polyphenols, GSH, and FRAP. GT also inhibited a significant rise in CK and XO activities induced by exercise. Furthermore, GT decreased the AST activity and hypoxanthine and UA concentrations before and after exercise. Consumption of GT, a beverage rich in polyphenols, may offer protection against the oxidative damage caused by exercise (46).

Caffeine is considered a very popular, extensively ingested substance among the general population and athletes or recreational exercisers. There are favorable relations between coffee use and liver outcomes and a wide range of other health outcomes, while, there are no decisive deleterious relations with any health outcomes, except for pregnancy. Caffeine has beneficial effects in several features of exercise such as extended aerobic-type activities, fixed-term activities, brief duration activities, high-intensity prolonged exercise as in team sports, and strength/power activities. It does not cause harmful changes in urination, water loss, sweating rate, and fluid balance. In periods of sleep deprivation, it can improve vigilance and alertness (47). Caffeine is an effective ergogenic aid for sustained maximal endurance activity, and has also been shown to be very effective for enhancing time trial performance. Recently, it has

been demonstrated that caffeine can enhance, not inhibit, glycogen resynthesis during the recovery phase of exercise (48).

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3. Conclusion

The use of performance-enhancing substances, particularly Anabolic-Androgenic Steroids (AAS) and Selective Androgen Receptor Modulators (SARMs), represents a growing public health concern. While historically associated with competitive athletes, doctors alarms about a surge in usage among teenagers. Despite being marketed for their tissue selectivity, SARMs still exhibit adverse side effects strikingly similar to traditional AAS, including severe testosterone suppression, cardiovascular strain, and altered lipid profiles. Most concerning, however, is the significant risk of drug-induced liver injury (hepatotoxicity), which has been widely documented with both AAS and SARM use. Similarly, consumers must exercise extreme caution when using under-researched herbal supplements, as their active compounds and potential toxicity are often unknown. However, it is crucial to distinguish between harmful drugs and safe, effective supplementation. Caffeine, green tea, creatine remains one of the most rigorously researched dietary supplements available. Creatine monohydrate, for instance, has been clinically proven to enhance muscle growth and athletic performance without subjecting the human body to the dangerous side effects associated with hormonal enhancers.

Disclosure

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