Anabolic Steroid Effect on the Liver

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Abstract

Anabolic steroids are synthetic derivatives of testosterone shown to increase muscle size and strength. Chemical substitutions on the testosterone molecule cause increased potency and duration of action. The 17-α-alkylation modification allows steroids to be taken orally, but the slower clearance in the liver makes them more hepatotoxic. The frequency and severity of side effects depends on several factors including the formulation of the drug, route of administration, dosage, duration of use, and individual sensitivity and response. Anabolic steroid users tend to take supraphysiologic doses or multiple steroids and other drugs simultaneously which increases risk of adverse effects. Hepatotoxicity can be seen as elevated liver transaminases, acute cholestatic syndrome, chronic vascular injury, hepatic tumors, and toxicant-associated fatty liver disease, as well as significant changes in lipoproteins. Many of these changes will stabilize or reverse with cessation of steroid use, but some can be life-threatening. Over-the-counter supplements can be contaminated with anabolic steroids, causing hepatotoxicity in unsuspecting consumers.

Background

Testosterone is the endogenous male sex hormone with anabolic and androgenic effects. Increased muscle mass and strength through increases in protein synthesis and nitrogen fixation lead to the anabolic effects, and the development of male secondary sexual characteristics is a result of the androgenic effects (1,2). In the unmodified state, testosterone is metabolized rapidly and must be administered intramuscularly, sublingually, or transcutaneously (3).

Anabolic steroids are synthetic compounds that are structurally related to testosterone, bind to androgen receptors, and exert masculinizing as well as anabolic effects to varying degrees (2). They also have a longer duration of action, are more bioavailable, and attempt to maximize the anabolic effects and minimize the androgenic effects of testosterone on muscle and other tissues (1,2,4,5). Anabolic steroids are available in oral, parenteral, topical, and sublingual forms (2,6). They are medically indicated for male primary or secondary hypogonadism, aplastic anemia, bone marrow failure, and treatment of patients with human immunodeficiency virus infection or acquired immunodeficiency syndrome who have muscle wasting, depression, or fatigue (1,4,7). They also have been shown to be effective as performance-enhancing agents and thus have been subject to "off label" abuse by athletes for more than 60 years (8,9). Supraphysiologic doses of testosterone ethanthate have been shown to increase fat-free mass, muscle size, and strength in normal men with or without exercise (4). The anabolic effects are more profound when resistance exercise is added (4) which has likely led to the increased popularity of anabolic steroids among weight lifters over the past few decades (6).

Testosterone has a therapeutic index of 1, meaning there is similarity in proportion between the anabolic and androgenic effects (10). The synthetic steroids attempt to maximize the anabolic effects while minimizing the androgenic effects. For example, stanozolol has a ratio of 30/1, making it much more anabolic than androgenic (6). Although modifications in structure are made in synthetic steroidal compounds to emphasize the anabolic properties (11), all have both androgenic and anabolic effects (2,6).

The anabolic steroids likely work through three main effects (5). First, they enhance the body's utilization of protein creating a positive nitrogen balance and turning on protein synthesis to build muscle mass (12). Second is a proposed anticatabolic effect. Glucocorticoids depress protein synthesis and anabolic steroids may have the ability to block or displace glucocorticoids from binding to their receptors resulting in a net gain of muscle mass (5). However, this mechanism has not been equivocally demonstrated (13). Third is a psychologic effect. Steroids may cause increased aggression allowing the user to intensify their training, indirectly increasing muscle size and strength and to be more aggressive during competition (14,15).

There are two main chemical substitutions to testosterone which occur in the formulation of synthetic steroids (3). Esterification of the 17-β-hydroxyl group makes the molecule more hydrophobic and longer lasting (2,3). Duration of action can be further enhanced if injected in an oily solution (2). This is used in testosterone cypionate, enanthate, and

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1537-890X/1703/97–102
Current Sports Medicine Reports

propionate to increase potency and duration of action through delayed absorption (2,3). The second modification, resulting from 17-α-alkylation, reduces hepatic metabolism which allows these steroids to be administered orally (3). The oral steroids are resistant to immediate degradation, but the slower clearance from the liver makes them potentially more hepatotoxic (1,2). The potency of the oral steroid as a group tends to be less than the injectable steroids (16). Some of these same 17-α-alkylated derivatives also are available in parenteral forms which can make them also hepatotoxic (1). Alkylation at this C-17 position of testosterone alters the relative anabolic potency in relation to the masculinizing effects (3). Removal of the 19-methyl group is another chemical substitution seen in the potent anabolic steroid 19-nortestosterone (nandrolone) which has increased anabolic activity and based on positive tests is quite popular among users (10).

The number of users and frequency of illicit anabolic steroid use is difficult to obtain. There may be as many as 3 million anabolic steroid users in the United States and although illicit steroids are thought to be mainly used by athletes, studies have shown that 70% to 78% of users are noncompetitive bodybuilders and nonathletes using these drugs for cosmetic purposes (6,17–19). Users are often hesitant to approach physicians so information regarding various anabolic steroids are often circulated among users through gyms, underground publications, the internet, and trainers (2).

The frequency and severity of anabolic steroid side effects depend on several factors including the formulation of the drug, route of administration, dosage, duration of use, and individual sensitivity and response (2). Users tend to take dosages well above therapeutic recommendations to achieve supraphysiological concentrations of testosterone or testosterone derivatives and may practice "stacking," which involves taking multiple types of anabolic steroids at the same time, often including both oral and parenteral formulations (10,20,21). This technique may include other drugs to enhance the anabolic effects or avoid unwanted side effects from the various steroids including human chorionic gonadotropin, antiestrogens, aromatase inhibitors, 5-alpha reductase inhibitors, diuretics, and insulin (17,18). Users may take anabolic steroids in a cyclic pattern, using them for several weeks or months alternating with periods of nonuse (10). Other users will administer the drugs in a pyramid or step-up pattern where dosages are steadily increased over several weeks followed by a step-down period and transition to off cycle or a different set of drugs (21). Users taking anabolic steroids for appearance purposes rather than athletic performance may not cycle in the same way strength athletes often do. These users may use anabolic steroids at supraphysiologic levels for years without cycling off and can display behaviors consistent with substance dependence disorder (10,21). These practices, along with use of other drugs, can jeopardize the athlete's health by increased risk of significant side effects on several organ systems (2,3).

Anabolic steroids are classified as schedule 3 drugs by the U.S. Drug Enforcement Agency and are generally obtained by users illegally (22), but have been found in tainted over-the-counter supplements advertised for increasing energy, muscle mass, or virility sold legally in many countries (23,24). This can lead to significant side effects on unknowing consumers (24,25).

Studies of long-term use of steroids are difficult because there is often inconsistency in the production and concentration of the drugs, dosages used, and often use of multiple types of steroids concurrently (26,27). Prospective studies using the supraphysiologic doses of anabolic steroids often taken by users are difficult to get approved so most published studies of medical issues in anabolic steroid users are observational studies of unsupervised subjects self-administering the drugs (10), retrospective studies (17), case reports (28–30), or prospective studies using a single type of anabolic steroid at a nonsupraphysiologic dosage (4). It is important to note that there are differences in the side effects associated with anabolic steroid use under medical supervision versus unsupervised use and simultaneously taking multiple drugs at high doses (10). A recent meta-analysis on medically supervised prescription testosterone replacement therapy did not specifically mention hepatic issues in the adverse effects section (31). Therefore, this review will chiefly focus on the effects of supraphysiologic doses of anabolic steroids on the liver.

Hepatotoxicity

Since the liver is the primary site of steroid clearance, concerns regarding the toxic effects of chronic administration of anabolic steroids have been present since the early use of anabolic steroids in the 1950s (3). Anabolic steroids have been implicated in four distinct forms of liver injury (3,32–34): transient serum enzyme elevations (2,35,36), acute cholestatic syndrome (24,25,37), chronic vascular injury to the liver (peliosis hepatis) (38–40), and hepatic tumors including adenomas and hepatocellular carcinoma (41–45). The esterified injectable steroids, including testosterone cypionate and testosterone enanthate, seem to have few adverse effects on the liver and have only rarely been implicated in causing cholestasis (37), but their long-term use may increase the risk of hepatic tumors and nodular transformation (41–45). Orally administered steroids, which have the 17-α-alkyl group modification, are generally well tolerated, have limited virilizing activity, and have been extensively evaluated as a means of increasing weight gain and muscle development in catabolic states, as well as improve athletic performance (26). However, they have been shown to have more adverse effects on the liver compared with the parenteral administration of esterified testosterone (37). Overall, considering the presence of millions of illicit anabolic steroid users, the number of reports of hepatotoxicity is quite low (6).

Transient Serum Enzyme Elevations

Steroid use is often associated with an increase in plasma activity of liver enzymes (26). Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), lactate dehydrogenase (LDH), and gamma glutamyl transpeptidase (GGT) are present in higher concentrations in hepatocytes. An increase in plasma levels of these enzymes reflect hepatocellular damage or at least increased permeability of the hepatocellular membrane. Steroid-induced, transient elevation of the enzyme levels are reported to generally be in the range of two to three times normal in asymptomatic subjects (26). Dickerman et al. (36) found that exercising subjects in their study had elevations of creatine kinase (CK) and AST, but not GGT, consistent with

muscle damage from exercise independent of steroid use. Aspartate aminotransferase is a better marker of muscle damage than ALT (46). People with hepatic damage will have elevations of the enzyme specific to the liver, GGT along with AST and ALT, but not CK (36). Many bodybuilders who use steroids are larger, stronger, and exercise with greater intensity compared to nonusers. Bodybuilders or resistance training athletes using anabolic steroids who show elevations of AST and ALT may simply be having mild rhabdomyolysis, rather than steroid-inducted hepatotoxicity (2,36). Therefore, reports of hepatotoxicity based on serum enzyme elevations alone may be overestimated. Most athletes taking anabolic steroids to increase muscle size and strength follow intense resistance training regimens to maximize their effects. This intense training leads to muscle damage and enzyme leakage which may be confused with hepatic damage (36,47). Elevations of AST and ALT can be seen with heavy exercise, but in the presence of CK elevation and absence of GGT elevation, liver damage due to anabolic steroids cannot be diagnosed (35,36). Physicians often fail to acknowledge the potential role of muscle damage in enzyme elevations, leading to overemphasis of anabolic steroid-induced hepatotoxicity based on transient serum enzyme elevation (36).

Acute Cholestatic Syndrome

A particular form of acute cholestasis, which can be severe requiring hospitalization, has been linked to the use of anabolic steroids (24,28,30,48–50). The 17-α-alkyl substituted steroids have decreased first-pass hepatic metabolism and are known to provoke a highly characteristic intrahepatic cholestasis via their direct toxic effects (50). The liver injury is generally noted within 1 to 4 months after initiating steroid use, but may be delayed as long as 24 months (30,48,50). The onset is usually insidious with development of nausea, fatigue, and pruritus followed by dark urine and jaundice (50). This bland type of cholestatic injury shows significant bilirubin and alkaline phosphatase elevation but only mild aminotransferase elevation, indicating minimal hepatocellular injury (50) despite the presence of jaundice (30). Liver biopsy often shows a bland cholestasis with minimal inflammation and typically absent or mild hepatocellular necrosis or bile duct injury (30,48). The hepatic dysfunction is usually reversible, (50,51), but jaundice and pruritus can be prolonged even after the anabolic steroids are discontinued (1). This clinical phenotype of bland cholestasis is so typical of anabolic steroid use that the diagnosis can be suspected even in someone who denies taking anabolic steroids or who is taking an herbal formulation or supplement that contains an unlisted anabolic steroid (30,48,49). Cholestasis is unlikely to be seen in patients receiving unmodified testosterone parenterally or topically (50). Management involves supportive care and symptomatic treatment of pruritus with antihistamines. Cholestyramine and ursodiol have been used for the cholestasis, but efficacy of these medications has not been proven (1,50,52). Corticosteroids should generally be avoided (1), but there has been a case reported where low-dose hydrocortisone was beneficial in lowering a recalcitrant bilirubin level (52).

Chronic Vascular Injury (Peliosis Hepatis)

Use of anabolic steroids has been linked to peliosis hepatis, a rare condition presenting with hypervascular lesions in the liver resulting in multiple blood-filled cavities in the liver parenchyma (3,40,53). There is usually an accompanying sinusoidal dilatation and loss of the normal endothelial barrier resulting in blood filled enlarged sinusoids and cysts either focally or throughout the liver (40,54,55). Patients are generally asymptomatic, but can present with right upper quadrant discomfort and hepatomegaly, or rarely with sudden abdominal pain and vascular collapse due to hepatic rupture and hemoperitoneum (38,40). Peliosis hepatis may be an incidental finding seen with imaging of the liver, during abdominal surgery, or at autopsy showing the liver to be enlarged, deep red in color, and fragile (3). Unless there are complications, there is no specific treatment for peliosis hepatis due to steroid use except supportive care, as the condition can at least partially reverse with cessation of steroid use (39,40).

Hepatic Tumors

A potentially serious complication of anabolic steroid use is the development of hepatic tumors, either benign hepatocellular adenoma (HCA) or malignant hepatocellular carcinoma (HCC). The liver is a hormone-sensitive organ with estrogen and androgen receptors (56), thus HCA and HCC can arise in the context of synthetic steroid intake, through use of either oral contraceptives or anabolic steroids (41,56).

These hepatic tumors typically develop in patients on long-term steroids, usually for aplastic anemia or hypogonadism (57), but occasionally, they are seen in athletes or body builders using steroids illicitly (1,41,58–60). Both parenteral and oral steroids may induce hepatic neoplasms, but there are rather strong indications that most anabolic steroid-related tumors of the liver are caused when the anabolic steroids containing a 17-α-alkyl group are used (60). Tumors are usually discovered after long-term use, but onset occurring after shorter periods of use have been described (41,58). The pathology of the tumors is usually hepatic adenoma, "well differentiated" hepatocellular carcinoma, or hepatic adenoma with areas of malignant transformation. Malignant transformation may occur in about 4.5% to 9% of cases and 4.2% of HCA will have an actual foci of HCC (58). Rarely, cholangiocarcinoma and angiosarcoma have been described in patients on long-term anabolic steroids (29). Additionally, HCC with testosterone receptors have been reported (44).

HCA are uncommon benign neoplasms, usually found in young women taking oral contraceptives (41), but a correlation between anabolic steroid use and HCA has been increasingly recognized (41,59). Hepatocellular adenoma and HCC have been described in patients taking anabolic steroids with no other evidence of liver disease and normal histology in the remaining parts of the liver (41,59,60). Hepatocellular adenoma with the β-catenin mutation, found more commonly in men, seems to be more likely to transform to malignant HCC (44,58). Larger tumors are more likely to transform, although malignant transformation has been reported in tumors < 5 cm (58).

Hepatocellular carcinoma is one of the most common malignant and widespread tumors worldwide making up 90% of primary malignant liver cell carcinomas (56). Males have higher liver cancer rates ranging from 4:1 to 8:1 with the majority arising from chronic liver disease and cirrhosis but long-term use of synthetic steroids have been described as a rare etiologic factor (10,56,57). Many of the case reports

have occurred in patients with other risk factors for cancer, such as chronic hepatitis C (61).

Clinical presentation is generally right upper quadrant discomfort and a hepatic mass found either clinically or on imaging studies. Routine liver tests are often normal unless there is extensive spread, rupture, or an accompanying liver disease (41). Hepatocellular carcinoma arising during anabolic steroid therapy is believed to have a better prognosis than those related to cirrhosis or chronic hepatitis B and C (61). Nonsurgical options should be considered because benign adenomas may show spontaneous regression in the tumor when the anabolic steroids are stopped, especially if detected early (1,57). Although not malignant, surgical intervention may be required due to sudden rupture and bleeding leading to life-threatening hemoperitoneum (41). Although most of the tumors developing by intake of oral contraceptives or anabolic steroids are benign, early detection of these lesions and serial ultrasound monitoring is important to avoid associated risk of possible malignant transformation and life-threatening hemorrhages (41,57). Enlargement and recurrence of tumors have been reported in cases where steroid intake has continued or been restarted (62,63).

Additional Forms of Liver Toxicity

Anabolic steroids may be a risk factor for toxicant-associated fatty liver disease (TAFLD) with users showing a rate over 12%, a 6-fold increase in risk even though they were younger and did not show signs of insulin resistance (64,65). The mechanism of development of this steatohepatitis is unclear although there are several possibilities including direct toxicity of anabolic steroids from long-term use (64,65).

Infectious diseases are a concern due to parenteral use of anabolic steroids and the possibility of needle sharing and other unsafe practices. An Australian study of steroid users found positive tests for both hepatitis C and hepatitis B, but there also were a large number of other risk factors beyond steroid use in the infected group and steroid injecting behaviors were not tied to the infections (66). The rates of infection were lower than found in users of other illicit drugs (66).

Anabolic Steroid Effects on Cholesterol

Anabolic steroid effects on cholesterol are concerning mainly from a cardiovascular perspective, but since the liver is central to the regulation of cholesterol levels in the body, it will be discussed here. While short-term use of anabolic steroids may not affect a user's overall cardiac risk since the effects on lipoproteins seem to be reversible upon discontinuation of the steroids (67), long-term and cumulative exposure are theorized to potentially have significant effects on cardiovascular risk, possibly through effects on high-density lipoproteins (HDL) (4,68) which has been recognized as an independent risk factor of cardiovascular disease (68). Injectable steroids tend to have a weaker effect on cholesterol levels as compared to oral steroids (69).

During anabolic steroid use the total cholesterol tends to stay the same or increase (70), while HDL-cholesterol demonstrates a marked decline below the normal range with reductions ranging from 39% to 70% depending on the type of steroid and amount taken (71). Studies have shown reductions of HDL-cholesterol down into the teens, which, based on Framingham data, places these patients at a three times greater risk for coronary artery disease compared with men with HDL above 50 mg/dL (68,71). Oral steroids increase the level of low-density lipoprotein (LDL) as does using multiple steroids at once, but since HDL is a primary scavenger of LDL particles, the LDL changes may be a secondary effect rather than a primary effect (12,71). The effect of anabolic steroids on triglycerides is not well known, but it is suggested that relatively low doses do not affect the serum triglyceride levels, while higher doses may elicit an increase (26). Of interest is that up to 50% reduction in lipoprotein (a), shown to have a close correlation with deposition in vascular walls, has been observed from steroid use (68,70). The cardiovascular effect of this steroid-induced reduction in lipoprotein (a) coupled with significantly decreased HDL is unknown (68). The exercise-induced effects of aerobic training on lipids do not seem to be able to offset the steroid-induced decline in HDL cholesterol (12). The effects of anabolic steroids on cholesterol and lipoproteins appear to be reversible, but can last for several weeks after use (67,71). Recovery time is dependent on the duration of steroid use (34). Although there is theoretical risk of cardiovascular disease due to effects on lipid from anabolic steroid use, an increase in overall mortality and cardiovascular events have not been documented in users of anabolic steroids at therapeutic doses (26,31,68).

Supplements and Liver Toxicity

There have been increasing numbers of case reports of liver injury due to bodybuilding supplements containing illicit oral steroids over the past few years (72). Rates of contamination of supplements vary but a recent review found overall contamination rates of supplements between 12% and 58% (73). Prohormones and steroids have been found in 14.8% to 25% of supplements analyzed (27,74,75). The true health consequences from adulterated supplements are unknown because adverse effects are likely underestimated and underreported. Additionally, some side effects are not acute events, but may result in delayed chronic health problems which may not be traced back to the supplement (76).

Even if the product is being sold legally, the mention of prohormones, natural steroids, or testosterone booster on the label of a supplement should raise concerns that synthetic designer steroids may be present in the product (23). Supplements are often mislabeled or use incorrect nomenclature of ingredients (23,27,77). Consumers may not realize they are taking an oral steroid so may take a product or multiple products consistently without taking a break or "cycling," which could lead to more side effects and toxicity due to long-term use of steroids (72).

Conclusions

Anabolic steroids can potentially cause a multitude of negative effects on the liver. These may include transient elevations of transaminases, acute cholestatic syndrome, chronic vascular injury to the liver (peliosis hepatis), benign adenoma and hepatocellular carcinoma, or TAFLD. Some of these conditions can have life-threatening consequences. There has likely been an overreporting of liver disease from steroid use based only on elevations of transaminases, which may simply be due to vigorous exercise. Adverse events have been most closely linked with the 17-α-alkylated testoster-

ones, although tumors also have rarely been associated with unmodified and esterified testosterone preparations. Chronic long-term or recurrent short-term use of anabolic steroids could potentially increase the risk of future atherosclerotic artery disease due to negative effects on lipoproteins, especially HDL and lipoprotein (a). Most side effects from steroid use eventually improve or reverse with cessation of use, but occasionally severe effects can remain. Users with preexisting liver disease are likely at higher risk for hepatic injury from use of anabolic steroids.

Supplements are readily available and commonly used by the athletic population. Due to lack of regulation they can be contaminated with substances not listed on the label which may include anabolic steroids. Clinicians need to be aware of the effects of anabolic steroids on the liver as patients may present with steroid-induced liver problems after unknowingly taking tainted over-the-counter herbals or supplements.

The author declares no conflict of interest and does not have any financial disclosures.

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