**The Clinical Applications of Anabolic Steroids**
*TAKE HOME: Testosterone and anabolic steroids are used to treat a myriad of diseases that are unrelated to and related to testosterone deficiency. Some examples are discussed in detail below.*

There are a variety of clinical applications for anabolic steroids, many of which are based around hormone-replacement therapy for a variety of diseases. Nevertheless, there are a variety of different forms of testosterone deficiency, including primary (caused directly by the production of insufficient amounts of hormone, which can be congenital), secondary (for example reduced testosterone production that is caused by a hypothalamic or pituitary tumor), and disruption that occurs in response to other clinical changes such as chemotherapy and radiotherapy [36]. Although testosterone levels decline during the course of normal aging, the use of testosterone and related agents in aging individuals is controversial.

Hypogonadism describes a condition in which individuals produce insufficient amounts of sex hormones (testosterone in males and estrogen in females). In males, the symptoms of hypogonadism include lethargy, anemia, fatigue, insomnia, weakness, changes in mood (irritability, depression, and dysthymia), erectile dysfunction, decreased libido, reduced muscle mass, and decreased motivation [36]. Therefore, hypogonadism plays roles in a variety of diseases and conditions. In this section we discuss the effects of anabolic steroids in a variety of both hypogonadism-related and -unrelated conditions.

***Coronary Artery Disease and Atherosclerosis***
*TAKE HOME: There is a large amount of evidence that a variety of cardiovascular diseases and their risk factors are associated with low testosterone levels in males, including adiposity and atherosclerosis. In addition, coronary heart disease might be more common in males with low testosterone levels. The use of testosterone replacement therapy exerts some beneficial effects in the cardiac system, such as reducing the levels of bad cholesterol and protecting against inflammation, which might help reduce the incidence of atherosclerosis and cardiac diseases.*

Coronary heart diseases such as coronary heart disease are some of the major causes of mortality and morbidity worldwide. The prevalence of these conditions increases with age, and they are more common in males than females. Therefore, some scientists have questioned whether sex hormones might play a role in their development and/or progression [134]. As discussed below in "**The Side Effects of Anabolic Steroids**", several studies reported that the use of many oral testosterone derivatives, such as 17-alkylated steroids, caused several risk factors for the development of coronary artery disease [145,146]. Nevertheless, males with low testosterone levels have many of the risk factors associated with heart diseases, including increased visceral adiposity, atherosclerosis, and hyperinsulinemia. In addition, some studies have suggested that males with coronary artery disease tend to have lower total testosterone concentrations and increased amounts of abdominal fat compared with healthy individuals [147]. Importantly, several studies have demonstrated that the intra-arterial administration of testosterone into the coronary artery causes it to dilate, rather than contract. Direct correlations between the size of coronary artery obstructions and reduced circulating testosterone levels have been reported [36]. Consistent with these observations, dozens

of epidemiological studies have been performed to assess the relationship between cardiovascular diseases and testosterone, and most of these have either revealed no relationship or have suggested that low levels of testosterone are associated with an increased prevalence of coronary heart disease. Importantly, none have suggested a causative role for testosterone in cardiovascular diseases [148].

Various cardiac diseases are associated with abnormal circulating cholesterol levels, and specifically high levels of total and low-density lipoprotein cholesterol (LDL-C; "bad" cholesterol), and low levels of high lipoprotein cholesterol (HDL-C "good" cholesterol). Some studies have suggested that overweight or obese males have reduced levels of both HDL and testosterone, and that treating these patients with testosterone increased HDL levels significantly [149]. However, these effects were not observed in all studies, and so the data must be interpreted with caution [36]. Nevertheless, other studies revealed that testosterone replacement therapy reduced the levels of LDL-C, total cholesterol, and triglycerides [150,151], and that these changes were of the highest magnitude in patients with the lowest baseline testosterone levels [152].

Although correlations between testosterone levels and other atherosclerosis-associated parameters (such as blood pressure, and clotting) have been reported, there are currently no data to support the clinical use of testosterone for the treatment of these conditions (for review see [134]). Nevertheless, the administration of testosterone did increase the levels of anti-inflammatory molecules in males with hypogonadism [153].

### Metabolic Syndrome, Type 2 Diabetes, and Obesity
*TAKE HOME: Metabolic syndrome encompasses a series of conditions including insulin resistance and obesity, and it often leads to type 2 diabetes. Many male patients with metabolic syndrome have low circulating testosterone levels. Some studies have revealed that treating both non-diabetic obese and diabetic individuals with testosterone and DHT improved insulin resistance and decreased fat mass, although other reports showed differing effects.*

Type 2 diabetes is a condition that arises when the body does not respond to insulin appropriately and so does not regulate glucose levels. Its prevalence is increasing worldwide concurrent with the increased incidence of obesity and the changing dietary habits. The main pathological presentation of type 2 diabetes is insulin resistance, whereby cells throughout the body (but particularly in the liver, skeletal muscle, and adipose tissue) are resistant to insulin and so do not respond appropriately. In many patients, metabolic syndrome is the precursor to type 2 diabetes. Metabolic syndrome is a broad term that encompasses a variety of conditions including insulin resistance, glucose intolerance, hypertension, inappropriate or abnormal circulating lipid levels, and obesity. It predisposes individuals to both diabetes and cardiovascular diseases.

Several studies have suggested that there are links between testosterone concentrations and glucose and insulin levels. Specifically, many reports revealed that testosterone levels were inversely correlated with insulin and glucose levels (so that glucose or insulin was high when testosterone was low and vice versa) in healthy subjects [154]. Consistent with this, patients with diabetes or metabolic syndrome had lower testosterone levels than did healthy controls [155,156]. Interestingly, some authors believe that hypogonadism might play a role in the development of type 2 diabetes, whereas other suggested that obesity might be the key player than links multiple related

conditions (low testosterone levels, cardiovascular disease, diabetes, and insulin resistance). However, data analyzing whether there is an association between testosterone and diabetes independently of obesity are controversial [134].

Several studies have assessed the clinical effects of treating non-diabetic obese males with testosterone and DHT. Importantly, a series of techniques used commonly to measure glucose tolerance revealed that both agents improved insulin resistance, which was accompanied by reduced central adiposity and decreased overall fat mass [157]. The effects of testosterone were more potent than were those of DHT, and the most beneficial effects were observed in males with low baseline testosterone levels. However, increasing levels too high (to so called supraphysiological levels) decreased glucose tolerance [134]. Similar studies have been performed in subjects with type 2 diabetes, including one that compared treatment using testosterone with that using insulin. Testosterone supplementation reduced the levels of glycated hemoglobin and insulin resistance significantly, and also decreased total cholesterol levels and waist circumference [158]. In contrast, other studies revealed that testosterone had no significant effect on these parameters, although this might be because testosterone levels were not increased sufficiently [159]. In addition, a meta-analysis of seven clinical trials was performed recently to assess the effects of the administration of testosterone to males with metabolic syndrome and/or type 2 diabetes. The resulting data did not support the routine use of testosterone in such patients with normal endogenous levels of testosterone because the effects on improving insulin resistance were only modest and there was no improvement in long-term glycemic control [160].

**The Side Effects of Anabolic Steroids**
*TAKE HOME: Although anabolic steroids are used clinically to treat a variety of diseases, the use of the same agents at much higher doses (such as those used by bodybuilders) can actually have negative and sometimes very serious or potentially fatal effects. This is likely because the doses used by these individuals can be 10- or 100-times higher than those used by physicians clinically. The list of potential side effects of anabolic steroids is very long. Here, we discuss some of these specific side effects, as well as the steps that could be taken to reduce the potential risks.*

As the use of anabolic steroids has increased over time, our knowledge of both their positive and negative effects has increased accordingly. As mentioned above, the use of therapeutic doses of anabolic steroids can treat a variety of diseases effectively. However, individuals using these agents for the purpose of building muscle mass must be aware of the difference between the therapeutic doses used by physicians and the supraphysiological doses used by bodybuilders, which are often 10- or even 100-times higher than the recommended or "safe" doses. Therefore, although some of the clinical uses listed above and the side effects listed here might seem contradictory, the differences in the doses we are referring to must be kept in mind. In addition, some of the illicit anabolic steroids used by bodybuilders have not been tested clinically and/or are produced and manufactured in conditions that are not pharmaceutical GMP certified or sterile. Furthermore, many steroid users obtain their knowledge from data sources that are heavily biased and/or written by steroid users or manufacturers, rather than medical professionals. As such, there is often a false sense of security that is guided by misinformation [168].

The use or abuse, and particularly the long-term abuse, of anabolic steroids is

associated with a series of adverse side effects that affect a variety of systems and functions, including behavior, the cardiovascular system, liver function, and reproduction. There have also been suggestions that long-term steroid use might adversely affect brain function. Nevertheless, many of the side effects depend on gender, steroid dose, the duration of administration, the individuals themselves, as well as the type of steroid used (for example, 17α-alkylated steroids, which are hepatotoxic). Here, we discuss the specific side effects of these agents and the steps that could be taken to reduce the potential risks.

### Glucose Metabolism and Insulin Resistance

*TAKE HOME: Although therapeutic (lower) doses of anabolic steroids might exert beneficial effects on parameters such as glucose metabolism and insulin resistance, there is significant evidence that the administration of much higher so-called supraphysiological doses might actually reduce glucose tolerance and induce insulin resistance. Therefore, any individual using doses of these agents at high concentrations should be monitored for symptoms of metabolic syndrome and diabetes regularly. Nevertheless, the data are complex and inconsistent results have been reported in different studies.*

As mentioned above in "**The Side Effects of Anabolic Steroids**", the data regarding the effects of testosterone in various disease states are highly complex and could seem contradictory. For example, a study performed in rats revealed that physiological doses of testosterone in hypogonadal rats improved insulin sensitivity, whereas supraphysiological doses equivalent to those used by bodybuilders actually reduced insulin sensitivity [191].

Another study administered supraphysiological doses of nandrolone decanoate to male rats, and then assessed the effects on glucose metabolism in the fasted state [192]. The authors stated that they selected this particular agent because it is the steroid used most frequently by athletes and bodybuilders [193]. In addition, rats were used to allow the investigators to identify direct effects without the interference that can be caused by endogenous testosterone from the same species in human studies [192]. Measuring parameters related to glucose metabolism in the fasted state is very important because this mirrors what might occur in humans overnight, which is when the body is most at risk from unnoticed potentially dangerous fluctuations in blood glucose. The rats were treated with a control solution, a therapeutic dose of nandrolone decanoate, or a supraphysiological dose of nandrolone decanoate once weekly for 8 weeks, and the effects of a variety of parameters related to insulin sensitivity and glucose metabolism were measured. The data revealed that serum glucose levels were significantly lower in rats that received the supraphysiological dose compared with those that received control or the therapeutic dose. These effects might be caused by reduced glucose utilization in tissues such as the liver and skeletal muscle due to increased insulin resistance [192]. Because exercise also reduces blood glucose levels owing to increased uptake into muscle, this study has potentially important implications in bodybuilders who use consistently high levels of these agents.

Several studies have assessed the effects of anabolic steroid use on glucose metabolism in humans. One study performed in 1987 measured glucose metabolism and the response of insulin to glucose in a cohort consisting of 10 sedentary non-obese males, six obese subjects, and 15 powerlifters. Of the 15 powerlifters, eight had taken

anabolic steroids for at least 7 years, whereas seven had never used these agents [194]. When the powerlifters that had and had not taken anabolic steroids were compared, glucose tolerance was reduced significantly in steroid users compared with nonusers, even though they exhibited higher postprandial circulating insulin levels. This suggests that insulin resistance resulted in impaired glucose tolerance [194]. Consistent with this, an additional trial assessed the effects of insulin in a cohort of males receiving methandienone, and revealed that individuals receiving the anabolic steroid had reduced glucose tolerance compared with control subjects [195].

However, another study in healthy young males suppressed endogenous testosterone production using a GnRH antagonist, treated the subjects with weekly doses of testosterone ranging from 25–600 mg for 20 weeks, and then assessed insulin sensitivity. The data revealed that there was no difference between individuals treated with the different doses of testosterone [196].

### *Cardiovascular Side Effects*
*TAKE HOME: Anabolic steroids cause a large number of cardiac side effects. Many of these are caused by atherosclerosis, blood clots, and hypertension, which subsequently cause a variety of major and potentially life-threatening cardiac events. Examples of the resulting conditions include heart attacks, stroke, irregular heartbeats, and a weak heart. Although many of these conditions can resolve when individuals stop taking the steroid, several can be fatal and occur without warning, even in seemingly healthy individuals. As such, significant caution is urged in individuals taking anabolic steroids, and particularly those taking supraphysiological doses.*

A huge variety of potential direct cardiovascular side effects of anabolic steroids have been reported in known or suspected users of anabolic steroids, many of which are described in detail below. In addition to all of these direct effects in the heart, anabolic steroids also cause a series of changes that affect the heart indirectly. For example, these agents increase the risk of atherosclerosis by inducing dyslipidemia, and these effects are more severe in patients that take oral 17α-alkylated steroids [197]. Similarly, anabolic steroids induce hypertension (high blood pressure), which also increases the risk of a variety of cardiac events [198]. Nevertheless, although the short-term negative effects of anabolic steroids are being understood increasingly, their chronic, long-term effects are still being elucidated [199]. Although we discuss the cardiovascular side effects separately here, there is a significant amount of overlap among these conditions, both in terms of their etiology and outcome. It is also important to note that there are dozens of cases to support an association between anabolic steroids and cardiac abnormalities, although only a small number of cases are listed here for the sake of brevity.

### *Myocardial Infarction*
Heart attack or myocardial infarction is caused by the disruption of the oxygen supply to the heart, which damages the heart tissue. Among the several cardiovascular events that have been linked to the use of anabolic steroids, myocardial infarction and associated sudden cardiac death have been reported in a number of patients. For example, a case report published in 1994 described the case of a male 31-year-old bodybuilder who took anabolic steroids and subsequently underwent myocardial infarction [200]. Consistent with this, a study describing the autopsy of two young males who died from myocardial infarction after taking anabolic steroids suggested a potential

association, although the authors stated caution and concluded that additional studies are needed to allow researchers and physicians to achieve a better understanding of the potential cause and effect relationship between myocardial infarction and anabolic steroid use [201]. Multiple other studies have described both fatal and non-fatal myocardial infarction events in similar individuals or populations [202,203]. At least some of these effects might be at least in part attributable to anabolic steroid-induced atherosclerosis, which is a known risk factor for myocardial infarction in healthy subjects, as well as in anabolic steroid users or suspected users [199,203].

*Cardiomyopathy*
The term cardiomyopathy translates literally into heart muscle disease. It generally describes a deterioration in the ability of the heart muscle to contract, which usually leads to heart failure. Common symptoms include swelling in the extremities (peripheral edema) and breathlessness (dyspnea), and untreated cardiomyopathy can often lead to an irregular heart rate and even sudden heart attack (myocardial infarction) and/or cardiac death [204].

A huge number of reports have linked the use of anabolic steroids with cardiomyopathy. For example, a study performed in 1991 linked steroid abuse with cardiomyopathy and subsequent sudden death in 22 athletes [83,205]. A recent case report described a case of cardiomyopathy in a 41-year-old bodybuilder who had been taking anabolic steroids and IGF-I for several years. Although the patient had no classical risk factors for cardiomyopathy, a thorough clinical workup revealed a variety of cardiac abnormalities including class IV heart failure, a dilated left ventricle (one of the four chambers of the heart), and a globally weak heart (known as hypokinesis) [206]. His condition was so severe that a workup for a heart transplant was initiated. Consistent with this, a large number of recent controlled studies have used various imaging modalities to compare the hearts of athletes and nonathletes that did and did not use anabolic steroids. Cardiomyopathy was a consistent finding in all of these studies in anabolic steroid users [207–209]. Although the severity of the resulting changes varied, the results of many of these studies suggested that the cardiomyopathy was at least partially reversible upon cessation of anabolic steroid use [83].

*Coagulation Abnormalities*
Coagulation abnormalities are a collection of disorders related to blood clotting. A number of clotting disorders have been linked to the use and/or abuse of anabolic steroids. A thrombus is the true medical term for a blood clot, which is formed by two components: a clot of aggregated platelets, and significant amounts of a protein named fibrin. Platelets are small cells within the blood that are critical for clotting to prevent bleeding. These clots can then lodge in blood vessels such as arteries (known medically as forming an embolism). A large number of reports have suggested that the abuse of anabolic steroids might induce platelet aggregation and thrombus formation, which is in part associated with dyslipidemia and hypertension [210]. For example, a study in weightlifters compared platelet aggregation in users and nonusers, which revealed that blood drawn from older users of anabolic steroids exhibited significantly more platelet aggregation compared with that from nonusers, which the authors concluded might explain the increased prevalence of thrombosis in anabolic steroid users [211].

Over subsequent years the link between anabolic steroids and platelet aggregation and embolism has been strengthened with improvements in the technology used to study the

links and also with an increased number of reports. For example, a study in 2000 reported the cases of two bodybuilders with thrombosis and embolism that caused a variety of cardiac events, including cardiomyopathy [212]. Many patients with anabolic steroid-induced coagulation abnormalities make a full recovery after the administration of anticoagulants and/or the discontinuation of steroids [83,213].

*Conduction Abnormalities*
The term "conduction abnormalities" is used to describe a collective group of abnormalities related to the electric impulses in the heart, which normally causes a heartbeat. During a regular heartbeat, electric impulses travel down both sides of the heart simultaneously, which causes both the left and right ventricles to contract. When vessels in the heart become blocked, for example in an individual with an embolism or atherosclerosis, the impulses become slowed in one side of the heart, which means that the two ventricles do not contract simultaneously. This can lead to cardiac arrhythmia, such as atrial fibrillation, or an irregular heartbeat.

There is significant evidence that anabolic steroids are associated with a variety of conduction abnormalities. For example, a report published in 1999 described the case of a young male bodybuilder who presented to the emergency room of his local hospital with an irregular heartbeat that was diagnosed as atrial fibrillation [214]. The patient's heart rhythm and symptoms resolved after he stopped taking the anabolic steroids. In another example, the thorough analysis of cardiac electrical stability in a cohort of weightlifters who did and did not use anabolic steroids revealed that anabolic steroid users had a significantly higher incidence of electric instability following exercise compared with nonusers [215]. This is particularly pertinent to individuals considering using anabolic steroids to build muscle mass because electrical instability can lead to a variety of cardiac events.

*Cerebrovascular Events*
Although cerebrovascular events do not involve the heart specifically, they are related to the cardiac system because they involve thrombus formation and embolism. The term cerebrovascular accident (sometimes termed cerebral infarction, cerebral hemorrhage, or stroke) describes the death of brain cells that is caused by blood clots preventing oxygen from reaching the tissue. Similar to myocardial infarction, cerebrovascular accidents are also a known side effect of anabolic steroids, and have been reported in a variety of patients including young adults [216,217].