Sports Endocrinology

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KEYWORDS

• Sports • Endocrine • Female athlete • Bone health • Osteoporosis • Osteopenia • Exercise • Diabetes

KEY POINTS

- Exercise has important health benefits for patients with diabetes but can also increase the risk of hypoglycemia.
- Strategies to adapt to exercise such as monitoring blood sugar, adjusting medications, and increasing carbohydrate intake are essential in patients with diabetes.
- Relative energy deficiency in sports is the new terminology for the Female Athlete Triad, which involves menstrual irregularity, low bone mineral density (BMD), and low energy availability in female athletes.
- Pharmacotherapy is typically not recommended for premenopausal athletes who have low BMD without a history of fractures or identified secondary causes of low BMD.
- Discussion of performance enhancing drugs should be part of wellness exams or sports physicals with athletes.

INTRODUCTION TO SPORTS ENDOCRINOLOGY

Sports endocrinology holds a unique importance in understanding and optimizing an active and healthy lifestyle. This special area of endocrinology focuses on the intricate hormonal responses that occur during exercise, training, and recovery, thus influencing various physiologic processes critical to physical activity and athletic training. This area of medicine is very broad with entire textbooks dedicated to it. This article will focus on the effects of exercise on blood sugar and diabetes, bone health, and topics unique to female athletes.

Exercise has a considerable impact on blood sugar levels. Physical activity enhances insulin sensitivity, allowing cells to better use glucose. Regular exercise helps regulate blood sugar, reducing the risk of diabetes, and managing the condition in those already diagnosed. Exercise has a significant impact on blood sugar. Therefore,

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special considerations for monitoring and adjusting medications may be necessary during episodes of increased physical stress.

Exercise plays a crucial role in the management and prevention of osteoporosis. Weight-bearing and resistance exercises, such as walking, jogging, and strength training, stimulate bone formation and enhance bone density. These activities also improve balance and reduce the risk of falls. Osteoporosis management involves a multifaceted approach that includes weight training, healthy diet, supplements, and prescription medications.

Regular exercise can positively influence the menstrual cycle by reducing menstrual discomfort, improving mood, and promoting overall well-being. However, excessive exercise without adequate nutrition may lead to irregularities or amenorrhea. Differential diagnosis, workup, and treatment of menstrual irregularities will also be addressed in this article.

The Female Athlete Triad (AKA: relative energy deficiency in sports [RED-S]) is a complex health condition with disordered eating, menstrual dysfunction, and low bone mineral density (BMD). Female athletes, particularly in high-impact or aesthetic sports, may experience this syndrome. The role of a multidisciplinary team in the management and treatment of this complex syndrome is of paramount importance. Anabolic steroids and other performance enhancers are popular and have significant side effects and complications.

EXERCISE AND DIABETES

Exercise influences blood sugar management in patients with diabetes, with major implications for both short-term glucose control and long-term metabolic health.[1] Heightened reliance on carbohydrates during exercise, especially at higher intensities, necessitates efficient glucose usage and management. For patients with diabetes, this means that physical activity can effectively lower and stabilize blood glucose levels, thereby aiding in the overall management of diabetes.

Regular exercise improves glycemic control in patients with diabetes through several different mechanisms, including increased GLUT4 transporter activity, increased glycogen breakdown, increased insulin sensitivity, and glycogen supercompensation.

With new or extreme exercise regimens, caution must be taken in diabetics due to an increased risk for cardiovascular disease, exercise-induced hypoglycemia, and musculoskeletal injury. It is particularly important to educate diabetic patients receiving insulin or secretagogue therapy regarding monitoring glucose levels and adjusting carbohydrate intake or medications with exercise.

One of the central mechanisms of glucose metabolism during exercise is the activity of the GLUT4 transporter.[2] During physical activity, GLUT4 transporters increase in number on the muscle cell surface, facilitating glucose uptake from the bloodstream into muscle cells. This activity fuels muscles while simultaneously lowering blood glucose levels.

Exercise increases muscle glycogen breakdown, particularly with high intensity activities.[2] This glycogenolysis, in turn, results in increased blood glucose uptake to replenishing glycogen stores, thereby lowering glucose levels in the bloodstream. After exercise, muscles become more insulin sensitive, further improving blood glucose control.

Glycogen supercompensation is another important response to exercise.[2] Glycogen supercompensation occurs following exercise, when muscles are able to store more glycogen than they had prior to the exercise. This increased storage capacity is crucial, not only for storing energy for future exercise, but for stabilizing blood

sugar levels in patients with diabetes. Fig. 1 describes how regular physical activity, regardless of type, can lead to a more stable glucose metabolism and lower A1C values.[3]

Sports-related Diabetes Treatment Considerations

- For patients with high cardiovascular risk, greater than 30 year-old (y.o.), or a previously sedentary lifestyle consider exercise stress testing and medical optimization prior to initiation of an exercise regimen.[3]
- Patients can use aerobic exercise, resistance training, or a combination of both in their exercise regimen with similar benefits and low risk.[3]
- Encourage 150 to 300 minutes per week of moderate-intensity or 75 to 150 minutes per week of vigorous-intensity exercise (or equivalent combination) for substantial health benefits.[4]
- In patients with diabetes requiring insulin therapy, increased carbohydrate intake is the mainstay for reducing the incidence of induced hypoglycemia.[5]
  - If the exercise duration is greater than 60 minutes, a 20% to 50% decrease in insulin dosing adjustment is reasonable.[5,6]
  - A simple regimen for carbohydrate replacement is 30 g of carbohydrates per hour of exercise.[6]
  - Due to increased risk of exercise-induced hypoglycemia, sulfonylureas and glinides should be avoided in patients on a regular exercise regimen.
- Measure blood glucose 2 to 3× prior to exercise to establish a baseline and closely monitor changes.[3]
  - If below 70:
    - Eat 15 g of fast-acting carbohydrates and recheck blood glucose in 15 minutes; only initiate exercise if blood glucose is higher than 90.
  - If between 70 and 90:
    - Patients with type 1 diabetes should consume 15 g of fast-acting carbohydrates and recheck blood glucose in 15 minutes, resuming exercise when glucose is higher than 90.
    - Patients with type 2 diabetes should consume 15 to 30 g of fast-acting carbohydrates and either immediately resume exercising if accustomed to starting at that blood glucose level or wait and recheck in 15 minutes if unaccustomed.
- If between 90 and 270, exercise is typically safe.
- Higher than 270:

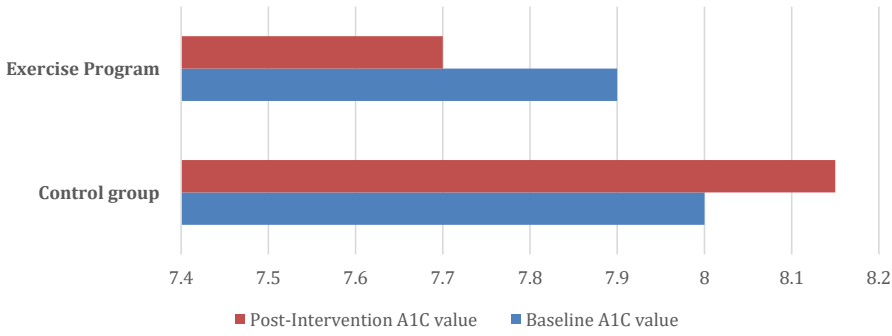

Fig. 1. Impact of 9 month exercise program on A1C in patients with diabetes.[13]

- Patients with type 2 diabetes should avoid exercise and medically address their hyperglycemia, either using short-acting insulin and measuring blood glucose 15 minutes later or seek medical attention, especially if symptomatic.
- Patients with type 1 diabetes should measure urine ketones and monitor for symptoms of diabetic ketoacidosis; they should seek emergency medical attention if one or more of the following are present with ketonuria.
  - Frequent urination and extreme thirst
  - Fatigue, weakness, or shortness of breath
  - Fruity-scented breath
  - Abdominal pain, nausea, or vomiting
  - Confusion

Summary

Overall, the physiologic changes induced by exercise offer substantial benefits for blood glucose regulation, particularly in diabetes. Through insulin-independent mediation reduction in blood glucose via the action of the GLUT4 transporter, increased glycogen use, glycogen supercompensation, and increased insulin sensitivity, exercise can effectively reduce hemoglobin A_{1c} and help reduce diabetic complications. Caution should be utilized when recommending exercise regimens to patients with diabetes, particularly those on insulin or insulin secretagogue therapy, with significant cardiac risk factors, long-standing diabetes, or a previously sedentary lifestyle.

BONE HEALTH FOR THE FEMALE ATHLETE

Introduction

While Sports Medicine involves the treatment of musculoskeletal injuries and performance optimization, it should also emphasize prevention and therapy for various orthopedic conditions. Low bone mineral density (BMD) is an important condition related to sports medicine and is more common in female athletes. Osteoporosis can increase the risk for injuries and significantly impact one's ability to stay active. While we traditionally think of athletes as young Olympic-caliber competitors, many Americans participate in athletic activities well into their seventh to eighth decade of life.

Osteoporosis is characterized by decreased BMD, structural deterioration of bone tissue, and heightened risk of fracture. Osteoporosis can be clinically diagnosed if an athlete has suffered a fragility fracture (even without measuring BMD) or if there is a T-score of -2.5 standard deviations (SDs), or lower at any site using dual energy x-ray absorptiometry (DEXA).

In the United States, a clinical diagnosis may also be based on the Fracture Risk Assessment Tool (FRAX), which estimates the risk of a major osteoporotic fracture over 10 years, but only for women over 40 years of age. Both a 10 year risk of major osteoporotic fracture of 20% or greater or 10 year risk of hip fracture 3% or greater are consider high FRAX scores.[7,8]

Osteoporosis is typically asymptomatic but can present with pain from fragility fractures that occur with low kinetic energy injuries or activities that typically would not cause a fracture. Fragility fractures typically occur in the spine, hip, and pelvis but can also occur in the wrist, rib, or humerus.[9]

Imaging

Imaging for the diagnosis and monitoring of osteoporosis is typically performed via DEXA.[9] A T-score of 1 to 2.5 SDs below the young adult average is classified as low bone mass, or osteopenia, and a T-score of 2.5 SDs or greater below the average is

classified as osteoporosis.[7,8] The Z-score compares a patient's BMD to that of their age group. A Z-score of −2 or lower indicates a BMD that is significantly lower than expected for that age.[9] Pediatric athletes can be diagnosed with osteoporosis if they have either a vertebral compression fracture OR a Z-score less than −2 AND a history of significant fractures that occur with low energy sports injuries. Examples of qualifying significant fractures include 2 fractures of the long bones before 10 years of age or 3 such fractures before 19 years of age.

Approach for Premenopausal Athletes

Routine osteoporosis screening through BMD is generally not advised for premenopausal female athletes with the exception of those with known secondary causes for osteoporosis or a history of fragility fractures.[10] It is essential to evaluate and ensure calcium and vitamin D intake and levels and to assess exercise habits in all premenopausal women experiencing low bone mass. After reviewing medical history, physical examination, and initial laboratory test results, further testing and/or specialty referral may be necessary.

Generally, pharmacotherapy is not recommended for premenopausal athletes who only have low BMD without a history of fractures or identified secondary causes of low BMD. In those women, it is reasonable to ensure adequate calcium and vitamin D intake and schedule another BMD test in 1 to 2 years.[11,12] Women with a low BMD who show signs of continuing bone loss upon subsequent BMD assessments should be referred to a sports specialist with knowledge of metabolic bone conditions for further evaluation and treatment.[13]

Individuals with osteoporosis who experience fractures of the spine or hip and those with multiple fragility fractures should start pharmacologic treatment with BMD reassessment in 1 to 2 years.

There is a paucity of evidence to guide the pharmacologic treatment of premenopausal osteoporosis and referral to an endocrinologist, preferably with expertise in treating athletes, is recommended. For most premenopausal women with osteoporosis who qualify for pharmacologic treatment, starting bisphosphonates is recommended, with teriparatide as an alternative option.[14] Bisphosphonates and teriparatide can improve BMD in several types of premenopausal osteoporosis, but studies are small and do not provide evidence regarding fracture risk reduction. When considering the use of bisphosphonates or teriparatide for treating premenopausal osteoporosis, it is important to weigh the possible short-term and long-term risks, including those related to potential pregnancy.[15]

Approach for Postmenopausal Female Athletes

Postmenopausal female pharmacotherapy is recommended when osteoporosis is diagnosed due to a T-score of −2.5 or less, or a fragility fracture. If a treatable secondary cause is identified, it should be addressed accordingly. Additionally, postmenopausal women with a T-score between −1.0 and −2.5 and a high fracture risk might be considered for pharmacologic treatment, especially if their 10 year probability of a hip fracture or a major osteoporotic fracture is 3% or 20%, respectively. If the results show stable or improved BMD, the treatment should continue, and further BMD measurements can be taken every 2 to 5 years (depending on the clinical scenario).

Oral bisphosphonates are recommended as first-line treatment of postmenopausal female athletes with osteoporosis. Alendronate is often preferred because of its proven effectiveness in decreasing the risk of both vertebral and hip fractures, as well as evidence suggesting continued benefits in reducing fractures even after completing a 5 year treatment period.[16] Risedronate is as a suitable alternative to alendronate.[16]

Denosumab is a viable substitute for those who are not suitable for or cannot tolerate bisphosphonate therapy. This is often preferred over anabolic agents (teriparatide, abaloparatide, or romosozumab) for initial treatment.[16,17] For competitors unable to use oral bisphosphonates, intravenous bisphosphonates can be considered.[18]

There is some debate about the best initial treatment for active, postmenopausal women with a particularly high fracture risk, such as those with a T-score of −2.5 or lower and fragility fractures, a T-score of −3.0 or lower without fragility fractures, or a history of severe or numerous fractures. Some experts recommend starting with an anabolic agent due to its potent bone-building effects, while others favor bisphosphonates for initial treatment because anabolic agents are generally more costly, require subcutaneous injections, and have less long-term safety data available.

For sportswomen with a very high risk of fracture who did not start treatment with an anabolic agent, a switch to an anabolic therapy is recommended when initial treatment is ineffective.[19] After anabolic therapy is discontinued, patients should be treated with an antiresorptive agent (typically a bisphosphonate) to preserve the gains in BMD from anabolic therapy. For individuals who are unable to tolerate oral or intravenous bisphosphonates, denosumab, or raloxifene may be prescribed instead.[20]

THE FEMALE ATHLETE TRIAD (RED-S)

Introduction

A healthy high-performing female athlete has the necessary caloric intake to support energy demand and physiologic function while providing a sufficient balance between availability of energy in the form of calories, body function metabolism, and healthy menstrual cycle. In 2014, the International Olympic Committee changed the diagnostic definition from the female athlete triad to RED-S to adapt a more holistic view toward the pathologic diagnosis involving menstrual irregularity, low BMD, and low-energy availability.[21] Ultimately, low caloric energy intake or excessive caloric energy expenditure can cause maladaptive pathophysiologic and hormonal pathways that cause amenorrhea, improper bone development, and a variety of other signs and symptoms that lead to overall poor health outcomes.[11]

RED-S is usually seen in physically active girls and young women. It can occur in athletes of any sport and competition level, but is more common with gymnastics, figure skating, swimming, track and field, and rowing.[22,23] It is important for primary care physicians (PCPs) to identify athletes are risk for this triad so timely evaluation and interventions can be implemented.

Evaluation, Diagnosis, and Guidelines for RED-S

The overall incidence of RED-S is very ill defined for a variety of reasons including the variability of patient presentation and patient reluctance to provide a full, accurate history. It is important to recognize in evaluation that the athletes at highest risk for RED-S are those who participate in sports that emphasize a lean body structure and endurance, such as cheerleading, swimming, gymnastics, dance, and long-distance running.[24] The most common presenting symptoms include increased musculoskeletal injuries such as sprains and strains, infertility with menstrual irregularities, poor athletic performance due to decreased energy, and stress fractures secondary to low BMD. Due to these pathologies most commonly presenting in adolescence and early adulthood, the long-lasting effects of RED-S can include permanent infertility, lifelong disordered eating, osteoporosis, and psychiatric disease.[13] Recognition of those populations at highest risk of RED-S is essential to avoid these long-term life-altering presentations.

Screening and diagnosis of RED-S is very challenging as the symptoms can present slowly and subtly. However, a clinical assessment tool to assist medical professionals in identification and management does exist.[25] It is recommended that screening be completed as part of annual sports physicals and especially when an athlete presents with eating disorders, unusual weight loss, underweight body mass index, lack of normal growth or development, menstrual irregularity, or decreased sports performance of unclear cause.[26] If an athlete presents with these symptoms or there is high clinical suspicion based on patient presentation, it is recommended to undergo screening with laboratory and imaging workup.

The diagnosis of RED-S is largely clinical at first presentation with identification of the previously discussed phenotype and characteristics. However, based on clinical judgment of severity, further workup can be pursued by the clinician. Laboratory abnormalities that may be seen are consistent with decreased energy availability and hypogonadotropic hypogonadism including hypoglycemia, low leptin, low luteinizing hormone, low estrogen, low growth hormone, elevated cortisol, and decreased Z-score consistent with low BMD on DEXA.[27] If these laboratory abnormalities and symptoms of energy deficiency are present, it is recommended for the patient to continue training with a multidisciplinary treatment plan in place and follow-up every 1 to 3 months to assess compliance. Furthermore, if more serious features of disease such as anorexia nervosa, presence of extreme weight loss techniques leading to hemodynamic instability, or severe electrocardiography abnormalities such as bradycardia are present, that athlete should immediately cease all training with a written contract and begin a treatment program.[26]

Menstrual Disorders in RED-S

Menstrual disorders are a hallmark of RED-S. The most common menstrual disorders associated with sports are primary amenorrhea, secondary amenorrhea, and oligomenorrhea. The differential diagnosis is broad for these conditions, so ruling out other etiologies is essential.[28] Primary amenorrhea is defined as absence of the first menstrual period during normal development and evaluation for this disorder should occur if the patient has not menarche by 3 years after thelarche or by 15 y.o. or absent pubertal development by age of 13 years.[29] Secondary amenorrhea includes regular menses interrupted by the cessation of menses for 3 months or irregular menses interrupted for 6 months. Infrequent menses with intervals greater than 45 days in adolescent competitors and 35 days in adult athletes is oligomenorrhea.[30]

Evaluation of Amenorrhea

Evaluation of menstrual disorders in athletes is best done in consultation with a gynecologist. The most common causes of amenorrhea are structural, endocrine (eg, hypothalamic or pituitary disorders, primary ovarian insufficiency), sequelae of chronic diseases, or induced.[30] Initial laboratory testing includes ruling out pregnancy. In addition to a thorough history and physical examination, diagnostic tests are typically needed to determine the cause of amenorrhea. Serum total and free testosterone can be utilized to evaluate for hyperandrogenism. To assess endocrine etiologies, tests should include thyroid-stimulating hormone, prolactin, follicle-stimulating hormone, and luteinizing hormone. Elevated levels of anti-Mullerian hormone may indicate polycystic ovary syndrome or functional hypothalamic amenorrhea, while low levels indicate primary ovarian insufficiency rather than menopause. Transvaginal ultrasound can identify structural causes of amenorrhea (eg, polycystic, ovarian tumors) and MRI can be used to identify brain tumors.

Role of Primary Care and the Multidisciplinary Team

PCPs are uniquely positioned to educate patients, athletes, and coaches about RED-S during sports physicals and annual examinations. PCPs should be mindful of the common and subtle examination findings as they are most often the first medical professional patients present to for amenorrhea, fatigue, and musculoskeletal injuries. They should also be familiar with the clinical criteria and workup needed to diagnose the disease. It is imperative that PCPs educate colleagues about RED-S so it can be diagnosed more frequently and appropriately. Furthermore, PCPs can assist in changing the cultural barriers in sports and society that may lead to RED-S being underdiagnosed in the female athlete population.

Clinics Care Points

- There is little evidence to guide premenopausal osteoporosis and treatment should include referral to an endocrinologist or bone density specialist, preferably with expertise in treating athletes.
- Initial treatment of RED-S is typically non-pharmacologic and requires a multidisciplinary approach.
- Treatment of RED-S should focus on increasing energy intake through dietary changes and/or decreasing energy expenditure through training regimen modification.
- The overall goal of RED-S treatment is weight gain, increase in energy intake with decrease in expenditure, resumption of normal menses, and recovery of BMD.

PERFORMANCE ENHANCING DRUGS

Introduction

Performance enhancing drugs (PEDs) are agents used as an attempt to gain a competitive advantage. It has spread from professional sports to fitness and recreational sports. The majority of users are now recreational athletes.[31] Advantages may be in the form of increasing muscle mass and appearance in body building, strength in power lifting/explosive sports, and increased long distance performance in endurance sports such as triathlon. The World Anti-Doping Agency is the main organization that oversees policies and determines the list of substances and methods that are banned from competition.

PEDs include

1. Anabolic steroids, hormones that increase lean muscle mass, strength and decrease fat mass, are the most common used agents.[31]
2. Androgen precursors such as dehydroepiandrosterone (DHEA).
3. Human growth hormone (HCG).
4. Eythropoietin (EPO).

Discussion

Almost all androgens have been used as PEDs and include testosterone, trenbolone, 17-alpha androgen (oral), and boldnone (veterinary drug).[32] Most supplements can be purchased online or prescribed medically and legally such as testosterone for male hypogonadism. Some of the more potent steroids are procured through covert exchanges that are not regulated by the government or are purchased as veterinary grade medications.[33] Athletes will take these drugs as escalating doses over about 12 weeks (pyramiding) or by combining with 2 more steroids (stacking). Some stacks will include opposing drugs to counteract side effects, such as HCG with an anabolic to oppose testicular size reduction.[33]

DHEA is a precursor to testosterone and advertised in various fitness and body-building magazines. It is not androgenic but converted to testosterone and is touted to raise serum concentrations.[34]

HCG has effects on body composition as it increases muscle mass, strength, and greatly decreases fat. HCG binds to luteinizing hormone receptors and stimulates testes to secrete testosterone.[35]

EPO, which stimulates red blood cell production and thus increasing the oxygen carrying capacity, gained notoriety with the Tour de France. Prior to the popularity of EPO, athletes would train in hypoxic conditions such as at altitude and then transfusion their own blood prior to competition.[36]

Complications

While improving performance, there are many complications associated with these substances. Cardiac hypertrophy has been well documented in the literature with cases of sudden cardiac death due to myositis or hypertrophy.[37] Adverse effects on lipids such as major increase in low-density lipoprotein (LDL) and decrease in high-density lipoprotein (HDL) are well known.[38] Steroids have also been found to profoundly clotting factors leading to increased risk of thrombosis.[39] Severe erythropoiesis, leading to further risk of thrombus is also known.[40] Hypogonadism following discontinuation occurs in about 21% of men taking steroids.[41] Perhaps the most well-known complication is the neuropsychiatric side effects of severe aggression, depression, and even suicidal ideations.[41]

Summary

PEDs have made their way from professional into recreational sports. While there are many products on the market, the more well-known products are anabolic steroids, DHEA, HCG, and EPO. While they do enhance performance, there are many detrimental side effects and complications to their use.

CLINICS CARE POINTS

- Sports medicine physicians should have knowledge of the substances that are banned by various sporting organizations.
- Discussion of PEDs should be part of wellness examinations or sports physicals with athletes.
- Athletes who wish to stop using these substances should be encouraged but will need education that they will become temporarily hypogonadal.
- If athletes continue to use PEDs—cardiovascular, endocrine, hematopoietic, and psychiatric complications need to be considered and monitored.

DISCLOSURE

The authors have nothing to disclose.

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