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Management of the female athlete triad

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Abstract

The female athlete triad (FAT) is defined by the American College of Sports Medicine (ACSM) as low energy availability (low EA), functional hypothalamic amenorrhoea and osteoporosis. In low EA, lutein dysfunction first develops, followed by anovulation and, subsequently, oligomenorrhea, leading to amenorrhea. Moreover, low estradiol concentrations due to amenorrhea decrease bone mineral density (BMD). In athletes with one of the factors of FAT, the risk of a stress fracture is 2.4–4.9 times higher and may increase the risk of fracture throughout the lifespan. Low EA is the starting point of FAT, and the FAT concept emphasizes the importance of energy intake that is commensurate with exercise energy expenditure in athletes. In amenorrheic athletes who undergo gynecological examination, it is important to appropriately evaluate whether the cause is low EA and to review exercise energy expenditure and energy intake. It remains difficult even for experts to calculate available energy using the ACSM definition formula when evaluating energy deficiency. Moreover, performing early FAT screening during teenage years and cooperation between the department of obstetrics and gynecology and sports dietitians are also issues. The aim of this paper is to review the management of FAT from the viewpoint of gynecologists.

Key words: amenorrhoea, female athlete triad, low energy availability, osteoporosis, stress fractures.

Introduction

Following the recent successes of female athletes, expansion of competitions and successful bid for the Tokyo Olympic and Paralympic Games 2020, there has been a greater focus on supporting female athletes and on medical science to improve their competitiveness. An increasing number of reports have especially highlighted the female athlete triad (FAT), which is characterized by low energy availability (low EA), functional hypothalamic amenorrhoea and osteoporosis.[1] FAT is common in this population and therefore requires the accumulation of data as well as the creation of preventive methods and management guidelines for gynecologists. The Japan Society of Obstetrics and Gynecology issued management guidelines for female athletes in 2017 to appropriately evaluate low EA, which is the starting point of FAT. A system for gynecologists to coordinate with sports dietitians and psychiatrists and provide treatment is also under development. Although several studies have been published on FAT, to our knowledge, few reports exist from the viewpoint of gynecologists. Therefore, we sought to review the evaluation and treatment of FAT from this viewpoint.

Concept of FAT and Relative Energy Deficiency in Sport (RED-S)

In 1992, the American College of Sports Medicine (ACSM) listed amenorrhea, eating disorders and osteoporosis as health problems of female athletes.[1] The ACSM subsequently defined these three diseases as FAT in 1997 and raised concerns about the condition.[1] In 2007, eating disorders were updated to low EA

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with or without an eating disorder. FAT is currently based on this ACSM definition.[1]

Furthermore, the International Olympic Committee (IOC) Consensus Statement Position Stand on the Female Athlete cited energy availability, menstrual function and bone health as health issues of female athletes in 2005.[2] The concept of RED-S was subsequently proposed in 2014. It indicated that a state of relative energy deficiency in all athletes, including male athletes, causes generalized adverse effects (e.g., development, metabolism, mental condition, circulatory organs and immunity), resulting in decreased performance. This resulted in the publication of a joint statement concerning the importance of energy balance.[2] The concept of RED-S proposed by the IOC includes FAT and is a broad concept, including male and female athletes. These concepts emphasize the importance of energy intake that is commensurate with exercise energy expenditure in athletes.[1,2]

Factors composing FAT

Low energy availability (EA)

As previously mentioned, low EA, one of the current definitions of FAT, was defined as an eating disorder until 2007.[1] It has been widely reported that female athletes have a higher incidence of eating disorders than women in the general population.[3] This is especially common in athletes in their teens and early 20s.[3] The incidence of eating disorders is high in athletes participating in aesthetic-type sports such as rhythmic gymnastics and gymnastics, endurance-type sports such as long-distance track and field, and weight class-type sports such as judo and wrestling.[3] Researchers have reported that the incidence of eating disorders in elite athletes is 18–31%, compared with 5–9% among women in the general population.[3] Furthermore, the attempted suicide rate in athletes with eating disorders is 5.4%.[3,4] When comparing the incidence of eating disorders using the presence of menstruation, researchers found that the incidence was 11% in the normal menstruation group and 62% in the amenorrhea group.[5] However, it is too late to provide medical intervention after the diagnosis of an eating disorder. Early screening of athletes in a low EA state, which is the preliminary stage, and how to intervene at an early stage are important points when considering FAT prevention. In 2007, the ACSM changed the definition of low EA based on the presence of an eating disorder.[1]

EA is calculated by subtracting energy expenditure from energy intake.[1] Low EA is defined by the ACSM as less than 30 kcal per kg of free fat mass (FFM) per day. Loucks *et al*. investigated the relationship between EA and luteinizing hormone (LH) and found that periodic secretion of LH and amenorrhea is inhibited when EA decreases to less than 30 kcal/FFM kg/day; ACSM's definition of low EA is also based on these data.[6] To accurately calculate this low EA, it is necessary to accurately calculate energy intake and exercise energy expenditure. Sports dietitians generally confirm the results of a self-administered dietary record survey to calculate energy intake, but there are a few facilities where gynecologists can routinely request the evaluation of a sports dietitians. Furthermore, to accurately measure exercise energy expenditure, it is necessary to measure expiratory gas during exercise, but this is impractical. Therefore, in several cases, a method to calculate metabolic equivalents (METs) from the training menu is recorded by the athlete to calculate exercise energy expenditure. It is difficult for gynecologists treating amenorrheic athletes to measure energy intake and expenditure. To accurately measure FFM, it is necessary to measure total body composition using dual-energy X-ray absorptiometry (DXA), but facilities that can perform these measurements are limited. According to the ACSM, low EA is screened using a BMI of 17.5 or less in adults and 85% or less of estimated weight in adolescents.[1] The reason why estimated weight is used instead of BMI is because during adolescent years there are significant growth periods. In teenage athletes who have stopped growing, using BMI may be possible. In Japan, there is few data on the relationship between the estimated weight of athletes at puberty and amenorrhea. We refer to the current guidelines of ACSM, but because there are also differences due to race and body type, guidelines based on data from Japanese athletes are needed.

Hypothalamic amenorrhea

Loucks *et al*. examined the relationship between EA and LH and reported that the periodic secretion of LH is suppressed when EA decreases to less than 30 kcal/FFM kg/day.[6] In low EA, lutein dysfunction first develops, followed by anovulation and, subsequently, oligomenorrhea, leading to amenorrhea.[6,7] Luteal phase deficiency and anovulation were observed at a rate of 48% and 79% respectively, in runners running at least 2 h or 16 km/week for the past 12 months.[7,8] Female athletes are more likely to notice low EA than male athletes because of menstrual cycle abnormalities.

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LH values are an indicator of low EA diagnosis and amelioration; however, reference LH values for low EA diagnosis have not been defined.

Age at menarche

We performed a survey of age at menarche in 663 elite Japanese athletes and found that the mean age was 12.9 years. Furthermore, mean age (years old) at menarche by sport was as follows: gymnastics (16.9); rhythmic gymnastics (15.4); long distance (14.7); track and field, excluding long distance, (13.9); figure skating (13.8); synchronized swimming (13.5); badminton and soccer (13.4); swimming (12.7); skiing (12.6); short track (12.4) and speed skating (12.3). The age at menarche tended to be later for aesthetic-type sports.

Incidence of amenorrhea

The incidence of amenorrhea (7.3%) in athletes has been reported to be significantly higher in lean sports (11.7%), compared with women in the general population (2–5%).[3,9] It is also higher in lean sports than non-lean sports (11.7% vs 5.4%). In a study examining competition/event types, the authors found that the incidence of amenorrhea was high in ballet dancers, runners, gymnasts and figure skaters. In addition, they found that the incidence was 69% in dancers and 65% in long-distance runners.[3,9] An investigation of 1929 Japanese athletes showed that the incidence of amenorrhea was as follows: technical-type sports (2.7%), endurance type (11.6%), aesthetic type (16.7%), weight-class type (2.8%), ball-game type (2.7%) and instantaneous type (3.8%).

Few reports exist on the incidence of amenorrhea by competition level. An investigation of 2259 Japanese athletes and 490 control subjects by competition level reported that the incidence was 6.6% at the Japan national team level, 6.0% at the national competition level, 6.1% at the regional competition level, 2.6% at other levels and 1.8% in the general population control group nonsports-playing women. At the Japan national team level, the incidence of amenorrhea significantly increased, compared with the athletes in other groups ($P = 0.004$).

Osteoporosis

It has been reported that athletes have high bone mineral density (BMD) (5–15%), compared with women in the general population.[10] When examined by sport, bones of the lower extremities and lumbar vertebrae show high values at the load sites in volleyball and weight lifting players, whereas competitive swimmers show lower bone density compared with athletes who play other sports with a lack of load.[11,12] It has been reported that non-athletes with oligomenorrhea or amenorrhea have low BMD compared with those with eumenorrhea.[1,2,5,12,13] However, bone density has not been shown to be low in gymnasts with amenorrhea compared with those with eumenorrhea. It is possible that decreasing BMD due to low estradiol becomes masked in sporting events with certain characteristics where the impact is applied to the measurement site of BMD.[5] For this reason, it is necessary to measure the load and non-load sites in some sports/events. Researchers have also reported that amenorrheic athletes exhibited lower bone formation and bone absorption than those of a control group.[5] However, limited data exist on bone metabolism at puberty, and further research is needed. Low estradiol due to amenorrhea or low EA promotes bone resorption by osteoclasts and reduced BMD.[3,14,15] Moreover, low bodyweight may also decrease BMD.[3] Currently, the age of maximal bone mass acquisition is approximately 18–20 years, and if low estrogen status or low bodyweight is present at puberty, it is not possible to acquire maximal bone mass, leading to low BMD/osteoporosis.[5,16]

FAT and stress fractures

A stress fracture is caused by repeated application of a minor external force that does not normally cause a fracture; it is a typical disease of overuse syndrome. Factors affecting stress fractures are classified as internal factors such as body flexibility, skeletal alignment, BMD and hormones, and external factors such as training amount/intensity and technique.[17] Barrack *et al*. examined various factors related to bone stress injuries (BSI) and found that the most influential factor affecting BSI is training more than 12 h per week, for which the risk of stress fractures is 4.9 times higher.[16] Furthermore, several studies have evaluated FAT and stress fractures. When one of the three factors of FAT is observed, the risk of a stress fracture is 2.4–4.9 times higher, and the risk is 6.8 times higher when all of the factors of FAT are observed.[12] It has also been reported that the risk of stress fractures in amenorrheic athletes is two to four times higher than the normal menstrual cycle group.[3] In addition, the risk of stress fractures in athletes with low BMD is higher than those with normal BMD.[3,18–20] The risk of stress fractures is also higher in athletes with

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nutritional issues such as low EA.[3,21,22] It is assumed that FAT increases the risk of stress fractures because of low estradiol and energy deficiency resulting in an imbalance in bone metabolism. According to the ACSM guidelines, factors including age at menarche, menstruation, BMD and BMI are used to determine whether athletes can return to competition.[1]

Gender differences and age predilection

Although an examination of the incidence of athlete stress fractures has shown that there are no gender differences, other reports have found that the incidence is 1–3% in males and 10–12% in women and that it is higher in that patient population.[9] The incidence in elite Japanese female athletes is 11.7%, and the age predilection of stress fractures is reported to be 16–17 years.[23]

Incidence by sport/event

In a survey of 1961 Japanese athletes, researchers found that the incidence of stress fractures by sport characteristics was as follows: endurance type (e.g., long-distance track and field events), 26.4%; aesthetic type (e.g., rhythmic gymnastics), 24.5%; instantaneous type (e.g., swimming), 21.7%; ball game type (e.g., basketball), 16.5%; weight class type (e.g., judo), 11.3%; and technical type (e.g., archery), 8.7%. The incidence was the highest for endurance-type and aesthetic-type sports.

Incidence by competition level

In a survey of 2321 Japanese athletes, the incidence by competition level was as follows: Japan national team level, 14.8%; national competition level, 23.0%; regional competition level, 20.7%; and other levels, 17.5%. The frequency ranged from approximately 15% to 20% regardless of competition level.

Screening/Examination/Diagnosis

Medical questionnaire

The medical questionnaire based on the ACSM and IOC guidelines for screening the FAT is given in Table 1.

Table 1 Screening questionnaire for female athlete triad

1. When is your menarche?
2. When was your last menstrual period?
3. How long is your menstrual cycle?
4. Are you presently taking estrogens and/or progestins?
5. Have you ever missed a menstrual period for a year or longer during a teenager?
6. Is your BMI less than 18.5?
7. Are you always worried about your weight?
8. Have you ever had an eating disorder?
9. Have you lost more than 5 kg in the last 3 months?
10. Have you ever had a stress fracture?
11. Have you ever experienced low bone mineral density or osteoporosis?

*BMI is calculated: Body weight (kg)/height (m) × height (m)

Low EA diagnosis

Amenorrhea triggers a consultation with the department of obstetrics and gynecology. It is important to note whether amenorrhea is caused by low EA and it remains difficult even for experts to calculate available energy using the ACSM definition formula when evaluating energy deficiency. Further research is needed to examine screening methods for energy deficiency in Japanese athletes. Patients are currently diagnosed as energy deficient when BMI is less than 17.5 in adults, less than 85% of estimated weight in puberty and recent weight loss of ≥10% in 1 month.[1] There have been several cases of amenorrhea in athletes who do not meet these criteria. This may be caused by relative energy deficiency due to changes in weight and training amount/intensity. Menstrual cycle abnormalities of athletes are often classified into three types: (Type 1) participation in a sport where continuous low weight is required; (Type 2) weight loss is observed; and (Type 3) when the training amount and intensity is increased. The likelihood of determining whether amenorrhea is associated with low EA is high when patients meet one of these types. This can be found during an oral medical examination. In cases where these criteria are not applicable, several cases are caused by other diseases, including polycystic ovary syndrome.

When performing an oral medical examination, confirmation that the condition coincides with the above three patterns (excluding pregnancy) is necessary. Subsequently, after performing an internal examination and ultrasonography, hormone values should be measured (Fig. 1). At the very least, these should include LH, follicle-stimulating hormone (FSH), estradiol, prolactin, testosterone, thyroid-stimulating hormone (TSH) and free thyroxine (fT4).[1] The main characteristic of amenorrhea due to low EA is a decrease in LH. A low LH value is key to diagnosis. There are no specific diagnostic criteria for LH,

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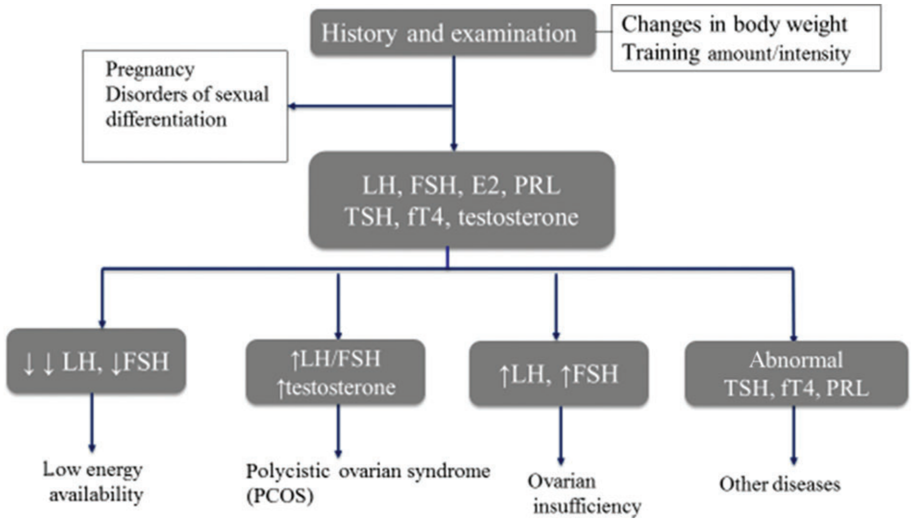

Figure 1 For diagnosis of amenorrhea due to low energy availability, we first exclude pregnancy. Next, we measure hormone values and perform an ultrasound to rule out other causes. The main characteristic is low luteinizing hormone (LH) level in amenorrhoeic athletes due to low energy availability (EA).

FSH and estradiol values when diagnosing patients with energy deficiency. However, when LH is 3 mIU/mL or less, the presence of energy deficiency is presumed. When amenorrhea due to energy deficiency is diagnosed, it is caused by an imbalance between energy intake from meals and exercise energy expenditure. It has been reported that total triiodothyronine (TT3) is low in athletes with amenorrhea. Attention should be paid to whether changes due to thyroid disease or amenorrhea are present.[3,7]

Low BMD/osteoporosis diagnosis

In 1997, ACSM formulated criteria on low BMD/osteoporosis in athletes based on the diagnostic criteria of the World Health Organization (WHO).[3] However, the diagnostic criteria of the International Society of Clinical Densitometry (ISCD) and ACSM slightly differ. It has been noted that the diagnostic criteria of ACSM was created from the viewpoint of athletes. Compared with the diagnostic criteria of ISCD, the diagnostic criteria of ACSM are stricter. Athletes are compared to non-athletes and it is assumed that their BMD is high. According to ACSM guidelines, the recommended BMD measurement site and diagnostic criteria for persons younger than 20 years and those aged 20 years or older differ; dual Energy X-Ray Absorptiometry (DXA) is used for diagnosis. In Japan, young adult mean (YAM) values are used to evaluate bone density in menopausal women. In the case of young athletes, especially teenage athletes before maximal bone mass acquisition, Z-score which is a comparison with the same age group – is used. Diagnostic criteria of The Japan Society of Obstetrics and Gynecology based on ACSM are shown in Figure 2. Evaluation of BMD is performed every 12 months.[3,24]

Younger than 20 years

Lumbar spine (AP) or whole-body imaging excluding the head is recommended as the measurement site.[1,24] Measurement of the hip (total hip or femoral neck) is not recommended for children because it is not reliable, and it is difficult to find bone landmarks in that population. The diagnostic criteria for low BMD is a Z-score of less than -1, and osteoporosis diagnosis both require a Z-score of less than -1, as well as one or more past fractures: long bone fracture of the lower extremities, vertebral compression fracture and two or more long-bone fractures of the upper extremities. Diagnosing patients with osteoporosis should not be based only on DXA results.

Aged 20 years or older

The lumbar vertebrae or femur, which are load sites, are recommended as measurement sites.[1] However, when it is difficult to measure these sites, measuring the distal 1/3 of the radius, which is a non-loaded site, is recommended. The diagnostic criteria for low BMD is a Z-score of less than -1 in patients older than 20 years. However, an osteoporosis diagnosis is considered in athletes with a history of Z-score of less than -2 and secondary causes of osteoporosis, such as amenorrhea. Athlete osteoporosis is diagnosed when a patient is 20 years or older with a history of Z-score of less than -2 and amenorrhea.

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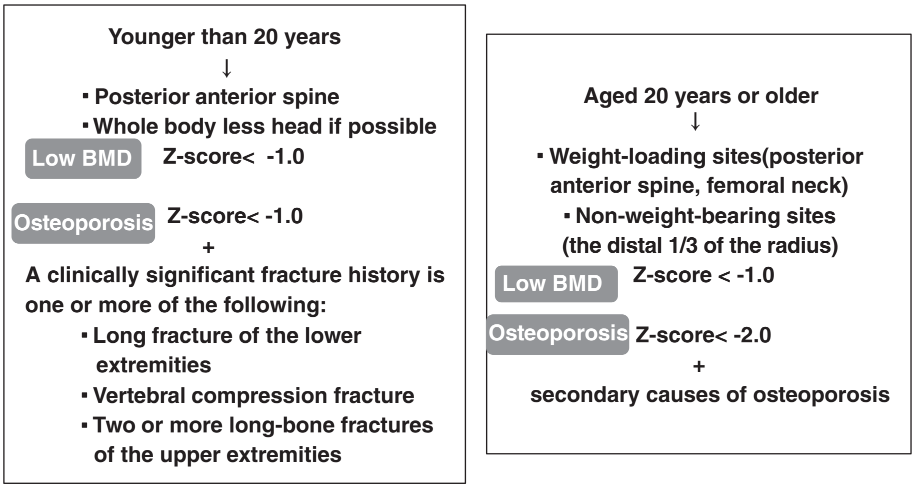

Figure 2 The clinical guidelines of The Japan Society of Obstetrics and Gynecology recommend criteria divided into younger than 20 years and aged 20 years or older based on ACSM definition for diagnosis of low BMD and osteoporosis in female athletes.

Treatment

Nutritional treatment

Treatment for amenorrheic athletes due to low EA is to improve low EA. In these cases, hormonal therapy is not the first-line treatment.

The key to increasing EA levels is to reduce exercise energy expenditure and/or increase energy intake from meals. Further research is needed to evaluate the cooperation between sports dietitians and coaches when reviewing the energy available. In Japan, there are no guidelines to concretely define the amount of food to eat to treat low EA. The ACSM recommends improving energy status on a daily or weekly basis, recovering menstruation on a monthly basis, increasing BMD on a yearly basis and performing the following to treat EA:

1. Recover recently lost weight.
2. Recover weight level to same as when menstruation was normal.
3. Increase BMI to 18.5 in adult or bodyweight to 90% in adolescence, or higher, of predicted weight.
4. Consume at least 2000 kcal/day or more, depending on the quantity of energy consumed for training; increase by 20–30% more than the amount of energy required to gradually increase BMI or body weight toward the target; and increase intake energy amount so that weight increases by 0.5 kg or more every 7–10 days.
5. Set EA to 45 kcal/kg/day or higher per kg of FFM.
6. Add 200–600 kcal of energy intake per day (when exercise energy expenditure is 2000 kcal/day)

In addition, the target carbohydrates intake recommended by the IOC is 3-5 g/kg body weight/day for low-intensity exercise, 5-7 g/kg body weight/day for medium-intensity exercise, and 6-10 g/kg body weight/day for high-intensity exercise.[25] When this does not lead to increases in EA or menstruation resumption, expert evaluation by a sports dietitians is necessary.

The IOC has issued guidelines to add 300–600 kcal to recent energy intake to improve low EA.[2] Clinicians should ensure that athletes understand RED-S, which was proposed by the IOC, and that low EA may cause decreased performance.

ACSM recommends a target BMI of 18.5 or higher. A survey of 1264 Japanese university student athletes showed that athletes with a BMI of 18.5 or lower had a significantly higher incidence of amenorrhea, compared with athletes with a BMI of 18.5 or higher. Thus, a BMI of 18.5 or higher is a reasonable value for FAT in Japanese athletes.[23]

Changes in LH levels are used as an indicator of improved low EA. Loucks *et al*. reported that the cyclic secretion of LH is not suppressed in cases where adequate EA can be secured.[6] There is a correlation between better EA and LH levels. We will examine the changes in LH levels while providing nutritional guidance for low EA improvement. Furthermore, we will continue to confirm the improvement of low EA values using LH values, similar to athletes who receive transdermal estradiol administration.

Hormonal therapy

As previously mentioned, treatment for amenorrhea associated with low EA is to improve low

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EA. However, it is difficult to resume menstruation when treating low EA in some sports/events such as long-distance running. In athletes who participate in these types of competitions, hormone therapy can also be used in combination with non-pharmacological therapy when LH values do not improve or menstruation is not resumed. It is important to continually work to improve energy status in these athletes and repeatedly educate the athletes. If menstruation does not resume after 1 year of nutritional therapy, ACSM recommends hormonal therapy if the patient is 16 years or older.[1] However, there is no evidence of the timing of intervention, dosage or administration route, including in athletes with late onset of menarche. The purpose of hormonal therapy is not only to prevent low BMD/osteoporosis but also to prevent adverse events, including those in the skeletal muscle and cardiovascular system, as well as psychological effects due to low estradiol. There is a focus on the influence on BMD, which is clinically problematic when considering FAT.

Weight gain is an effective treatment from the viewpoint of low BMD/osteoporosis. It has been reported that body weight or muscle mass is positively correlated with bone density.[12] However, no consensus exists on whether hormonal therapy via estrogen formulation increases BMD. ACSM guidelines also refer to data on Turner syndrome and anorexia.[1] Reports from other countries have indicated that oral estrogen administration inhibits insulin-like growth factor (IGF-1), which is necessary for the differentiation of osteoblasts in the liver.[1,26] In addition, oral administration is not effective in increasing bone density or reducing stress fractures, and IGF-1 is not inhibited by transdermal administration. Transdermal administration is effective for increasing BMD and has few side effects. It is the preferred method of administration, whereas oral administration of progestin is performed periodically. However, several issues such as insurance coverage, remain a problem in Japan. Estradiol formulations are used in patients with menopausal disorder. These medicines allow for the quantification of estradiol values. When performing daily administration, the competition and training schedule of the athlete is taken into consideration, as is withdrawal bleeding due to the oral administration of progestin. However, given that some athletes report lethargy at the time of oral administration of progestin, the administration schedule after considering the competition schedule and any other relevant factor is important. The administration of oral contraceptives/low-dose estrogen progestin (OC/LEP) in amenorrheic athletes due to low EA is not recommended as OC/LEP suppresses an already low LH level for a long period of time. This results in a loss of a reference LH level, and improvement of low EA cannot be evaluated. Furthermore, when OC/LEP is administered to amenorrheic athletes, side effects including bodyweight gain are often apparent. Because bisphosphonates are not safe for younger persons, they are difficult to use for young athletes.[3] Furthermore, selective estrogen receptor modulators (SERMs) are not recommended as they are doping-prohibited substances.

Summary

In amenorrheic athletes who undergo gynecological examination, it is important to appropriately evaluate whether the cause is low EA. If low EA is the cause, it is important to review exercise energy expenditure and energy intake. Moreover, performing early FAT screening during teenage years and cooperation between the department of obstetrics and gynecology and sports dietitians remain issues.

Disclosure

None disclosed.

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