The ancient Greeks barred women from participating at the ancient Olympics, even as spectators (1). Baron Pierre de Coubertin, the man credited for the birth of the modern Olympics, regarded women’s taking part in sports as being “against the laws of nature.” To cite his words: “Olympics are solemn and periodic exaltation of male athleticism, with internationalism as a base, loyalty as a means for its setting and female applause as a reward” (2). As a result of this attitude, women did not participate at the first modern Olympic games in Athens in 1896. However, a century later at the same place – during the 2004 Olympics, 4329 women from all over the world competed in the majority of 300 official events. Nowadays, taking part in sports is seen a positive experience for women, since it improves physical fitness, enhances self-esteem, and contributes to better physical and mental health. Apart from professional sport, there has also been a dramatic increase in women’s sports participation on recreational and amateur level.

Overuse Injuries in Female Athletes

Alan Ivković¹, Miljenko Franić², Ivan Bojanić³, Marko Pećina³

¹Center for Molecular Orthopedics, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA
²Department of Orthopedic Surgery, Dubrava University Hospital, Zagreb, Croatia
³Department of Orthopedic Surgery, Zagreb University Hospital Center and Zagreb University School of Medicine

The last three decades have witnessed a tremendous increase in female sports participation at all levels. However, increased sports participation of female athletes has also increased the incidence of sport-related injuries, which can be either acute trauma or overuse injuries. Overuse injuries may be defined as an imbalance caused by overly intensive training and inadequate recovery, which subsequently leads to a breakdown in tissue reparative mechanisms. This article will review the most frequent overuse injuries in female athletes in the context of anatomical, physiological, and psychological differences between genders.

> Correspondence to:
Miljenko Franić
Department of Orthopedic Surgery
Dubrava University Hospital
Av. Gojka Šuška 6
10000 Zagreb, Croatia
mfranic@kbd.hr

> Received: November 9, 2007
> Accepted: November 21, 2007

> Croat Med J. 2007;48:767-78
> doi:10.3325/cmj.2007.6.767
Injuries are an integral part of any sporting activity and they can be divided into two main groups: acute trauma and overuse injuries. Overuse injuries, otherwise known as cumulative trauma disorders, may be defined as tissue damage that is a result of repetitive demand over the course of time (3). It is not exclusively related to professional sports, but the term also refers to a vast array of diagnoses, including occupational, recreational, and habitual activities. Although injuries tend to be sport-related rather than gender-related, it has been noted that certain conditions, such as patellofemoral pain syndrome, stress fractures, or lateral epicondylitis are especially prevalent in female athletes (4).

Tremendous increase in female sport participation during the last three decades has offered scientists and clinicians valuable data on the physiologic and pathologic issues of the exercising female. This article will provide basic information on the most frequent overuse injuries in female athletes in the context of anatomical, physiological, and psychological differences between genders.

**Special characteristics of female athlete**

**Anatomical considerations**

**Bones and joints.** Compared with men, women have shorter and smaller limbs relative to body length. The length of lower extremities comprises 56% of the total height in men, compared with 51.2% in women (5). In the athletic disciplines where balance control is very important (e.g., gymnastics), shorter stature and wider pelvis give women lower center of gravity, which gives them substantial advantage. Additionally, wider pelvis can produce varus of the hips, increased femoral anteversion, and genu valgum resulting in an increased Q angle, which is known to be a predisposing factor for patellofemoral problems (6) (Figure 1).

**Muscles.** During prepubertal years, there is not much difference in muscle mass between...
boys and girls. During the puberty, however, because of the influence of the testosterone boys accumulate greater muscle mass. In adults, total cross-sectional area of muscles in women is 60%, compared with 80% in men (7). As a result, maximal strength measures and maximal power measures are reduced. Various other studies have shown that when only muscle quality is concerned, male and female muscle is not different. It appears, however, that the strength and power differences between the sexes are a function of muscle quantity and not only of their quality (8). Studies also showed that female athletes have increased hamstrings flexibility which could be responsible for increased anterior cruciate ligament (ACL) injury risk (9).

**Ligaments and joints.** Female athletes have increased general joint laxity than their male counterparts. It can be attributed to the more abundant joint capsule, as well as to the lower muscle mass that restrains the excessive joint movement in men (10). These observations are particularly true for the knee, ankle, and elbow joint. Several studies showed that joint laxity and hyperextension significantly increase the risk of ACL injury in female subjects (11).

**Physiological considerations**

Before puberty boys and girls do not differ much in terms of height, weight, heart size, or aerobic capability. After the stabilization of hormonal axis during the pubertal years, principal gender differences start to be more obvious. Proper estrogen serum levels are necessary for women to obtain maximum peak bone mass during the second and third decade (12).

Percentage of fat per body is another variable that is different in men and women. It is known that adult women have 22 to 26% fat per body weight and men have 12 to 16% (13). Androgens are responsible for greater lean body weight in men and estrogens are responsible for greater amount of fat weight. There was some speculation in the past that there is a critical level of body fat necessary to maintain normal menstrual function (14). Although this theory was not supported in the literature, it should be kept in mind that there is an individual threshold of body fat necessary for normal menstrual cycle.

For the same body weight, female athletes have smaller heart size than male athletes, lower diastolic and systolic pressures, and smaller lungs. This decreases female athlete effectiveness in both aerobic and anaerobic activities. Maximum oxygen consumption (VO2max) reflects body’s ability to extract and utilize oxygen, and is used as a measure for aerobic metabolism. It is known that VO2max is substantially lower in women than men, and even after accounting for differences in body weight and body fat percentage, there remains a gap of roughly 10%-15%. Recent evidence suggests that during heavy exercise, women demonstrate greater expiratory flow limitation, an increased work of breathing, and perhaps greater exercise-induced arterial hypoxemia than men (15).

**Psychological considerations**

Clinical observation has long suggested a link between the athlete’s personality and eating disorders. Anorexia and bulimia have thus been linked to personality traits such as introversion, conformity, perfectionism, rigidity, and obsessive-compulsive features (16). Furthermore, it should be noted that in most of the Western cultures athletic participation was always considered to be a man’s thing. Achievement, aggressiveness, and desire to win and conquer were traditionally considered as masculine, not feminine qualities. The widespread belief is that “the winning male athlete has just proved his masculinity, whereas the winning female often needs to justify her femininity” (17). This kind of prejudice, in combination with personality traits, may lead to de-
pression and anxiety episodes because a female athlete may feel she is not up to the perceived expectations of her sex. Female athletes have lower scores on dominance and confidence and higher on impulsiveness, tension, and general anxiety than male athletes (18). It should be noted that pressure to “win at all costs,” an overly controlling parent or coach, and social isolation caused by intensive involvement in sports may also increase the athlete’s risk for developing certain problems, such as eating disorders (19). These characteristics are known to be contributing factors in the development of eating disorders as an essential part of the female athlete triad syndrome which consists of eating disorders, menstrual dysfunction and osteoporosis.

Overview of most frequent overuse injuries in female athletes

Stress fractures

Stress fractures are relatively common overuse injuries, especially in athletes or military personnel. Although they are not exclusive to female athletes, this issue deserves a more detailed insight. There are two reasons for this: first, women in general have a higher incidence of stress fractures and, second, distribution of stress fracture sites seems to differ between genders. Stress fractures result from cumulative repetitive forces insufficient to cause an acute fracture. It has been noted previously that stress fractures occur more frequently in amenorrheic than normally-menstruating women (20,21). The exact mechanism of the development of stress fractures in amenorrheic women is uncertain and may not necessarily be related to low bone density. Menstrual status should be assessed in all female athletes who present with stress fractures.

Various studies have found that women have a higher incidence of stress fractures than men (22,23). Further studies consistently confirmed the fact that female recruits have a greater risk of stress fractures than their male counterparts, with the relative risk ranging from 1.2 to 10.0 (24). In the athletic population the risk ranges from 1.5 to 3.5.

Lower-extremity bones are most commonly affected, but stress fractures also occur in non-weight-bearing bones such as upper extremities and ribs. The tibia is the most commonly involved site for both men and women, but the fractures of the femoral neck, tarsal navicular, metatarsal, and pelvis are seen more commonly in the female athlete (25) (Figure 2). Evidence shows that cer-
tain stress fracture sites are reported more often in some athletes, eg, medial malleolus of the tibia and tarsal navicular stress fracture in high jumpers (26). The athlete with stress fracture presents with gradual onset of pain, aggravated by exercise. The hallmark of stress fracture is localized tenderness to palpation at the fracture site. Point tenderness may be best provoked over bones that can be easily palpated, such as the metatarsal bones or fibula. For bones that are deep, such as the pelvis or femoral neck and shaft, pain may be elicited through gentle range of motion or specific diagnostic tests. The combination of clinical picture and either bone scan or magnetic resonance imaging is sufficient for the diagnosis. The main treatment of stress fractures is rest from the offending athletic activity, a concept known as “relative rest,” and it is usually conducted as a step by step treatment algorithm (27). There is a group of stress fractures, called high-risk stress fractures, that requires additional treatment to “relative rest.” High-risk stress fractures include those in the femoral neck, patella, anterior cortex of the tibia, medial malleolus, talus, tarsal navicular, fifth metatarsal, and great toe sesamoids. General conditioning is maintained by exercising other areas of body and partaking alternative training, such as water running, swimming, or cycling. When patients do not respond to conservative treatment, surgical procedure should be advised.

**Patellofemoral pain syndrome**

Patellofemoral pain syndrome (PFPS) is a term used to describe painful but stable patella. It is a very common problem among female athletes, and the diagnosis of PFPS is made by exclusion of intra-articular pathologies, patellar tendinopathy, peripatellar bursitis, the plica syndrome, Sinding-Larsen-Johansson, and Osgood-Schlatter lesions (28). Anterior knee pain is possibly the most common symptom presenting in sports medicine. Other terms used in literature to describe pain-related problems in the anterior portion of the knee include patellofemoral arthralgia, patellar pain, patellar pain syndrome, and patellofemoral stress syndrome. Incidence of the PFPS in women is 20%, compared with 7.4% in men (29).

Radiological examinations are of great assistance in discovering anatomical deviations and irregularities in the patellofemoral joint. The increased incidence of PFPS in women compared with male athletes is thought to be related to structural, biomechanical, sociological, and hormonal differences between genders (30). Despite high incidence, etiology of PFPS still remains unclear. It still is unanswered what the cause of pain in PFPS is and which structure is involved. The causes of PFPS are usually classified as extrinsic and intrinsic, and three major factors contributing to the development of PFPS are lower extremity and patellofemoral malalignment, quadriceps muscle imbalance and/or weakness, and physical overload of patellofemoral joint (31). Many patients with marked patellar malalignment never experience pain, while others, with apparently no malalignment, experience problems.

Conservative treatment is effective in most patients. Quadriceps muscle stretches, balanced strengthening, proprioceptive training, hip external rotator strengthening, orthotic devices, and effective bracing will relieve the pain in most of the patients (32). If a comprehensive rehabilitation program of at least 6-month duration fails, surgical treatment should be suggested to the patient. There are several surgical procedures, such as lateral release, proximal patellar realignment, or medial/antomedial tibial tubercle transposition, that can be used for realignment of the patella in the trochlear groove and reduction of the patellofemoral pressure (33).
Patellar tendinitis – jumper’s knee

Patellar tendinitis (jumper’s knee) is a clinical entity characterized with anterior knee pain. Pain is aggravated by excessive strain on the extensor system of the knees after numerous jumps or long periods of running. Important causative factor was found to be the amount of training (both the amount of time and the amount of mechanical strain placed on the knee) that the athlete habitually carries out. The development of jumper’s knee also to a large degree depends on anatomical characteristics of the athlete, particularly of the lower extremities.

Pain as the basic symptom and a decreased functional ability of the afflicted lower extremity is a characteristic clinical picture of the jumper’s knee. The functional inability of the afflicted lower extremity is accompanied by intense pain and shows a range from slight to complete inability to participate in athletic activities. The most common site of tendinitis is around inferior pole of patella (34). Pećina et al (35) reported the appearance of pain at the insertion site of the patellar tendon at the tip of the patella in 80% of athletes suffering from jumper’s knee (Figure 3). In very rare cases, continuation of intensive athletic activities, despite the presence of evident symptoms of the disease, leads to a complete rupture of the patellar tendon. Kujala et al (36) reported that during a 5-year interval in a test sample of 2672 ambulatory patients with various knee injuries, 26.4% suffered from complications related to jumper’s knee. These findings led them to believe that jumper’s knee is the most common athletic injury to the knee.

Patellar tendinitis is relatively easy to diagnose, but its treatment is more difficult. Of the numerous treatments available, physiotherapy and correction of technical errors are often efficient. Surgical treatment is indicated if a prolonged and well-supervised conservative treatment program fails. Sclerosing injections or radical removal of the area with neovessels and nerves by arthroscopic shaving under ultrasound control has potential to reduce the tendon pain and allow the majority of patients to go back to full tendon loading activity within 2-month after surgery (37).

Lateral epicondylitis

A chronic overuse of the tendons at their insertion at the lateral humeral epicondyle is commonly called tennis elbow. The origin of the extensor carpi radialis brevis is always afflicted in the first 1-2 cm distal to its attachment to the extensor origin, and the origins of the other extensors are involved occasionally. It usually manifests between 30 and 50 years (but this condition may affect any age group) and women are more at risk than men. Lateral epicondylitis occurs in association with any activity involving repeated wrist extension against resistance. The main symptoms consist of pain and tenderness over the lateral humeral epicondyle. No single treatment has proven to be totally effective in the treatment of this condition. The treatment is usually non-operative and consists of pain relief and activity monitoring. Surgical treatment is required
in 5% to 10% of all patients and it can be performed either as an open procedure or arthroscopic procedure (38).

**Iliotibial band friction syndrome**

Iliotibial band friction syndrome (ITBFS) is one of the most common overuse injuries in runners, not only professional athletes, but also recreational joggers and other athletes whose activities entail a lot of running.

ITBFS is caused by many repetitive flexion and extension movements of the knee, during which rubbing of the band against lateral femoral epicondyle occurs (39). Friction occurs near foot strike, predominantly in the foot contact phase, between the posterior edge of the iliotibial band and the underlying lateral femoral epicondyle.

Sutker et al (40) reported ITBFS prevalence of 4.7% in 4173 injured runners, as well as a higher incidence of ITBFS in long-distance runners than middle-distance runners and sprinters. The dominant symptom is pain at the lateral side of the knee, aggravated by running. Pain is stinging in nature, and is located at the lateral femoral condyle 2 cm above the joint line. The treatment is usually non-operative and is based on modification of athletic activity, stretching exercises, and correction of predisposing factors. In recalcitrant cases of ITBFS, surgery has been advocated.

**Spondylolysis**

Spondylolysis is a common cause of back pain in female athletes. The most common localization of spondylolysis is fourth and fifth lumbar vertebra (41). The lesion usually occurs in the pars interarticularis (junction between the superior and inferior processus articularis) and may be unilateral and bilateral. Women who participate in sports such as gymnastics, figure skating, and dance may have additional risks (42). It is more common in sports that require episodes of hyperextension, especially combined with rotation. The fracture usually occurs on the side opposite to the one performing the activity. The athletes complain of unilateral low back pain, occasionally associated with some pain in the gluteal region. The pain is aggravated by movements involving lumbar extension. Occasionally, stress fractures to the pars interarticularis are asymptomatic. In cases with a recent onset of pain, x-ray may not demonstrate the fracture. In longer standing cases, special slanted oblique projections of the spine are taken, which, in positive cases form the shape of “Scottish terrier,” with an abnormally extended neck, indicating a defect in isthmus of the vertebral arch. When a spondylolysis is suspected clinically but plain x-ray is normal, isotopic bone scan or a single photon emission computed tomography (SPECT) scan should be performed (43). Patients with a positive SPECT scan result should then undergo CT scanning to image the fracture. The treatment is conservative and surgical fixation is very rarely indicated.

**Female athlete triad**

The female athlete triad was described and termed in 1992 by the American College of Sports Medicine, and consists of three interrelated disorders – eating disorders, menstrual disorders, and osteoporosis (44). The syndrome usually begins with disordered eating, and over the time low energy intake shuts down the hypothalamic-pituitary-ovarian (HPO) axis, leading to menstrual disorders and hypoestrogenism, which is ultimately responsible for decreased bone mineral density and osteoporosis (45). The obvious consequence of this cascade of interrelated pathophysiological events is greater risk of stress fractures.

**Eating disorders**

Eating disorders comprise a wide spectrum of disorders, ranging from occasional meal skip-
ping and calorie avoiding to anorexia and bulimia nervosa. The term “anorexia athletica” has been used to distinguish between true anorexia nervosa and disordered eating associated with training and sports performance (46). Risk factors for the development of disordered eating include western sociocultural norms, which attribute thinness to beauty, power, and control; psychologic factors such as poor coping skills, low self esteem, general anxiety, and depression; and gender factors – 90% of patients suffering from disordered eating are women (47). Another important risk factor is participation in certain athletic disciplines, such as ballet, figure skating, gymnastics, or distance running, which demand low body-weight and thinness of the competitors (Box 1). Engaging in severely limiting food intake, constantly weighing the foods, eating secretly, refusing to eat in front of others, and abusing laxatives impairs athletic performance and increases the risk of injury. Furthermore, it results in dehydration, malnourishment, and unhealthy weight loss, as well as psychological difficulties such as food/weight obsession, depression, and anxiety. The prevalence of eating disorders among female athletes is between 15% and 62% (48). In contrast, incidence in the general population is 1% (49).

Box 1. Sports that emphasize low body weight and body image of participants (3)

- Sports in which performance is subjectively scored – dance, figure skating, and gymnastics
- Endurance sports favoring participants with low body weight – distance running, cycling, cross-country skiing
- Sports using weight categories for participation – horse racing, martial arts, rowing
- Sports in which body contour-revealing clothing is worn for competition – volleyball, swimming, diving, running

Menstrual dysfunction

Eumenorrhea or normal menstrual function is dependent on the intact function of the pituitary gland, hypothalamus, ovaries, and endometrium. Cyclic nature of the process is maintained by precise secretion of both luteinizing hormone and follicle-stimulating hormone from the anterior pituitary, as a response to gonadotropin-releasing hormone arising in hypothalamus. Normal menstrual cycle lasts 25-35 days and may be divided into two phases. The first half of the cycle is the follicular phase, characterized by gradually increasing levels of estrogen, and the second half is the luteal phase, characterized by high concentrations of estrogen and progesterone.

The average age of menarche is 12.7 years in the USA and 13.5 years in some parts of Europe. It is known that female athletes who begin strenuous training before menarche occurs may experience a later menarche and have increased incidence of menstrual dysfunction than athletes who begin their training after menarche (50). This is very important because bone mass accumulation is the most intensive during puberty and the athletes with delayed menarche will have lower bone mineral density (BMD) and increased risk of scoliosis and stress fractures in the years to follow (51).

Amenorrhea is the most frequent type of dysfunction found in athletes and its prevalence varies from 3.4% to 66%, compared with 2% to 5% in the general population (44). Primary amenorrhea is defined as the absence of a menstrual cycle by the age of 14 without associated secondary sexual characteristics or by the age of 16 with these characteristics, whereas secondary amenorrhea is defined as the absence of menstruation for three consecutive months. Exercise-associated amenorrhea (EAA) is a subset of hypothalamic amenorrhea and is usually induced by synergism of low caloric intakes and intense training (52). Other factors such as weight, body composition, fat distribution, and mental stress must be considered as well. It is speculated that suppression and disorganization of pulsa-
tile luteinizing hormone release and complete suppression of leptin diurnal rhythm are underlying pathophysiologic mechanisms of EEA (53). It is thought that low-energy availability, combined with high levels of athletic activity, induces the hormonal changes, and the menstrual cycle is suppressed in order to conserve energy. EEA is a diagnosis of exclusion, and all the necessary diagnostic steps must be undertaken before it is made.

Estrogen protects the skeleton from bone resorption, and because of resulting hypogestrogenic state, amenorrhea is associated with premature bone loss and increased risk of both acute and stress fractures. Although the exact mechanism is still not fully understood, it is known that estrogen receptors are present on bone cells and directly increase osteoblastic activity (54).

**Osteoporosis**

Osteoporosis is defined by the World Health Organization (WHO) as inadequate bone formation and/or premature bone loss of more than 2.5 standard deviations below the average for young adults, resulting in low bone mass and an increased risk of fracture. However, it should be noted that International Society for Clinical Densitometry has published a position statement that the WHO guidelines should not be used for healthy premenopausal women (55). They also state that age-appropriate comparison scores (Z-scores) should be used instead of T-scores in the process of diagnosing osteoporosis in this population. Most of the bone mass is acquired during the adolescent years (especially during the pubertal growth spurt), and by the age of 18 most women have reached 95% of their peak bone mass. After peak mass is achieved, both men and women lose bone at a rate of 0.3% to 0.5% per year. It is known that bone tissue responds well to mechanical stress, and therefore, exercise combined with adequate nutritional intake is essential to attain peak bone mass in the adolescent female.

Amenorrheic young athletes may have failed to lay down sufficient bone mass or may have lost already accumulated bone mass (56). It is known that amenorrheic athlete may lose 2%-6% of bone mass per year, and develop the bone structure profile similar to that of the 60-year-old woman (57). Several studies showed that, amenorrheic athletes have significantly lower BMD at the lumbar spine, femoral neck, greater trochanter, Ward triangle, intertrochanteric region, femoral shaft, and tibia than healthy athletes (58). This kind of weakened bone puts her at 3-fold risk of stress fracture (59). Although BMD can be partially restored upon resumption of menstruation, studies showed that it still remains lower than in healthy athletes (60). Because of this partial irreversibility, it is crucial to identify all the athletes at risk as earlier as possible.

**Clinical evaluation and treatment of female athlete triad**

It is of utmost importance to educate athletes, coaches, physicians, and parents about the female athlete triad, so that they can readily recognize the symptoms and potential risks associated with this condition. The ideal time to screen for the triad is during the physical evaluation before sports participation, or at the beginning of the season in case of professional athletes (61).

An early diagnosis is the critical step in the prevention of immediate and long-term harmful health consequences. History should be detailed, and focus should be put on menstrual, nutritional, and body-weight history (62). General physical examination including basic anthropometrics measures such as weight, height, and subcutaneous fat thickness should be taken. Inspection should be focused on external signs of androgen excess, thyroid deficiency, and chromosomal abnormalities. The
most precise tool for determination of BMD is dual energy x-ray absorptiometry (63). It should be used in determining the amount of bone loss, but also in measuring the success of therapy.

Treatment should be based on a multidisciplinary approach (physician, registered dietician, and mental health practitioner) and should be focused on weight control and menstrual restoration. The first step of the treatment is to establish open and honest communication with the athlete, followed by setting common goals which include increase in the caloric intake and decrease in energy expenditure. This would restore normal menstruation and serum estrogen concentrations, and it would prevent further loss of bone mineral content. One of possible treatment schemes is the following: decrease training by 10% to 20%, increase the caloric intake, gain 2% to 3% of body weight, add resistance training, supplement calcium (1500 mg/d), and monitor using bone density scans (64). The use of hormone replacement therapy and oral contraceptive pills is not recommended in athletes with functional hypothalamic amenorrhea, since the increase in BMD is more closely associated with increase in weight than with hormone replacement therapy/oral contraceptive pills administration (65).

Conclusion

Female sports have come a long way. Women’s success in professional sports and the development of women’s professional sport teams is the evidence of the closing gender gap in athletics. Also, regular exercise is very important for obtaining general health, positive lifestyle behavior, and positive self-image, as well as learning such skills as teamwork, commitment, and goal setting. Combination of low energy intake, functional hypothalamic amenorrhea, and osteoporosis are the main constituents of the female athlete triad, which poses significant health risk to female athletes. If the symptoms of triad exist, early diagnosis and multidisciplinary approach are the essential aspects of the treatment of this disorder. It is of utmost importance that anyone involved in the training process of the young female athletes learns to recognize the signs and symptoms of this syndrome. Education remains the most important tool of prevention. In addition, preparticipation physical evaluation is the ideal time to identify athletes at risk and screen for any problems that may predispose the athlete to an overuse injury.

Acknowledgment

The authors thank Hrvoje Klobučar, MD, MSc from the Department of Orthopaedic Surgery, Medical School University of Zagreb for providing the figure of anatomic differences between genders.

References

11. Uhorchak JM, St Pierre P, Taylor DC. Risk factors associated with noncontact


doi:10.1210/jc.82.1.318

doi:10.1126/science.3388023

doi:10.1210/jc.2004-0712

doi:10.1016/S0279-8519(05)70044-1


doi:10.1001/jama.276.3.238

doi:10.1016/j.cocin.2006.05.007

doi:10.1016/S0277-8519(05)70044-1

doi:10.1080/11035784.10.13036049


doi:10.1530/eje.0.146045

doi:10.1530/eje.0.146045

doi:10.1530/eje.0.146045