Abstract:
It has been reported that the prevalence of amenorrhea in the general female population is 2-5% in young adult women, while this can be as high as 66% in certain sports events. Many investigations have found that prolonged amenorrhea in female athletes is associated with a reduction in bone mineral density (BMD). As exercise is an osteogenic stimulus in itself, it is possible that some bone loss due to amenorrhea may be offset in areas of high mechanical stimulus. However, BMD in female athletes is dependent on multiple factors and physical activity per se is not always protective for bone. Some of the factors that impact BMD include the nature of the sport discipline, the extent of energy deprivation, the changes in body composition and also various hormones. However, as the measurement of BMD represents only a static assessment of bone health, a more dynamic nature of the bone could be obtained by measuring the biochemical markers of bone formation and resorption. This review focuses on: 1) the impact of different mechanical loading on bone turnover markers in female athletes; and 2) the hormonal factors that influence these bone turnover markers. It has to be taken into account that the beneficial effects of increased mechanical loading from different athletic activities do not always appear to protect against the effects of possible amenorrhea on BMD in female athletes. Female athletes should be monitored at regular intervals to understand better the influence of a high training load on different hormonal markers that are responsive for the bone health in these athletes.

Key words: bone mineral density, bone turnover markers, estradiol, IGF-I, leptin, ghrelin, athletes

Introduction
Bone is metabolically active tissue with continuous remodelling occurring throughout its life. It is well known that physical activity is an important factor in attaining peak bone mass (Kohrt, Bloomfield, Little, Nelson, & Yingling, 2004). The type, intensity and duration of the physical exercise affect bone mineral density (BMD). The influence of high intensity exercise is of more importance on bone health and the effects of different exercises are more pronounced on the lumbar spine than on the femoral neck area (Wallace & Cumming, 2000). For example, Heinonen et al. (1995) suggested that resistance training provides a more effective osteogenic stimulus than endurance running. The basic mechanisms of these effects are not fully understood, especially in young female athletes participating in different sport disciplines. However, a normal ovulatory cycle is necessary (Petit, Prior, & Barr, 1999). It is well known that female athletes with an irregular menstrual cycle run a risk of decreasing BMD to such an extent that stress fractures may occur under minimal impact loading of the bone (Cumming, 1996). This demonstrates the importance of specific sex hormones on BMD values in young female athletes.

In addition to specific mechanical loading, different body composition parameters may have an influence on the BMD in young female athletes. Fat-free mass (FFM) appears to be one of the main predictors of different BMD values in healthy premenopausal women (Jürimäe, J. & Jürimäe, T., 2007). The significant positive relationship between BMD and FFM indicates that athletes involved in weight-bearing activities with such loading characteristics exhibit greater BMD compared with non-athletic controls (Heinonen et al., 1995). In addition to the importance of FFM, fat mass (FM) is also an important determinant of BMD in premenopausal women (Reid et al., 1992). Although the precise mechanism has not been specifically clarified, different hormonal factors have been postulated to be involved with mechanisms between FM and BMD (Abou Samra, Hwalla, Baba, Torbay, Dib, & El-Hajj Fuleihan, 2005; Jürimäe, J. & Jürimäe, T., 2007). For example, insulin and insulin-like growth factor-I (IGF-I) through the insulin receptor have a positive effect on BMD (Ogata et al., 2000). Another factor...
that may play a role in the FM and BMD relationship
is leptin (Abou Samra et al., 2005; Jürimäe, J. &
Jürimäe, T., 2007). Accordingly, in addition to
specific sex hormones, other hormonal factors are
also involved in the development of BMD in young
female athletes.

This review focuses on the bone turnover mark-
ers in young female athletes with different sport
participation and the possible hormonal mechani-
isms that mediate the development and mainte-
nance of BMD in these athletes. In addition, as
many young female athletes are at great risk of de-
veloping amenorrhea as a result of the needs of spe-
cific sport disciplines, factors that determine which
young female athletes are likely to develop amen-
orrhea and its effects on bone metabolism will also
be discussed.

**Bone turnover markers in young female athletes**

Different mechanical loading in young fe-
male athletes and associated bone modelling and
remodelling should be associated with increased
levels of bone turnover markers, and hypoestro-
genin in athletes with amenorrhea could cause a
further increase in the bone resorption markers
(Misra, 2008). The utilization of different markers
of bone turnover is a unique addition to the use of
BMD in examining female athletes. However, one
of the limitations of using markers of bone forma-
tion and resorption is that these markers represent
an average of turnover from all skeletal sites in the
body and consequently are not site-specific. It is
also possible that these markers are affected by di-
urnal variation (Creighton et al., 2001). However, it is important to note
that while these markers have certain limitations,
they are much more descriptive of the dynamic na-
ture of bone tissue than a dual-energy X-ray absorp-
tiometry (DXA) scan, which provides a more static
representation (Creighton et al., 2001).

Few investigations have been performed on fe-
male athletes in which both BMD and bone meta-
 bolic markers were evaluated. For example, Mat-
sumoto, Nakagawa, Nishida and Hirota (1997)
reported higher total body BMD and urinary py-
ridinoline and deoxypyridinoline (bone resorption
markers) values in judoists than in long-distance
runners and swimmers. In contrast, there were no
differences between these groups in serum pro-
collagen type I C-peptide and bone alkaline phos-
phatase (bone formation markers) values. However,
it could be suggested that to experience an increased
BMD, elevations in bone formation would be nec-
 essary to overcome the increased bone resorption.
Accordingly, Creighton et al. (2001) reported that
athletes involved in the high-impact sports (basket-
ball and volleyball players) displayed greater values
of serum osteocalcin (a bone formation marker) as
well as the higher BMDs at weight-bearing sites
compared to athletes participating in non-impact
sport (swimmers) and control subjects. In contrast,
swimmers had reduced serum osteocalcin values
compared with basketball and volleyball players
as well as with the untrained controls. In addition,
the measured BMD value of individuals involved
in non-impact sport was significantly lower at the
hip (trochanter and femoral neck) than in women
who participated in high-impact sports but not dif-
f erent from the untrained controls. Therefore, no
differences between the studied groups were found
in the cross-linked N-telopeptide of type I collagen
(a bone resorption marker) values (Creighton et al.,
2001). In another study, O’Kane, Hutchinson, At-
ley, and Eyre (2006) by measuring urinary cross-
linked N-telopeptide as a bone resorption marker
and urinary C-telopeptide of type II collagen as a
cartilage degradation marker investigated whether
differences in skeletal stresses in female athletes
undergoing high-intensity training for diverse types
of aerobic sports affect their bone metabolism. It
appeared that both biomarkers, for bone and car-
tilage degradation, showed significant differences
between rowers, cross-country runners and swim-
ners. The results suggested that rowers undergo
the highest bone remodelling and runners the high-
est cartilage degradation, while swimming clearly
stresses the entire body, but apparently not the
skeleton in a way that stimulates bone remodelling
(O’Kane et al., 2006).

Proteau, Pelle, Collomp, Benhamou, and Cour-
teix, et al. (2006) study provided, for the first time,
analysis of bone metabolic status combined with
BMD measurements and the effects of weight
cycling on the balance between bone formation
and resorption in female judoists. Precompetition
weight loss resulted in a net increase in bone re-
sorption. Specifically, C-terminal telopeptide of
type I collagen was released into the circulation
during bone resorption and has been thought to be
the marker of bone resorption with the highest con-
tribution from the bone (Seibel, Eastell, Gundberg,
Hannon, & Pols, 2002). Interestingly, serum osteo-
calcin (a bone formation marker) values increased
non-significantly three weeks after the weight loss
episode in female judoists (Proteau, Pelle, et al.,
2006). However, to what extent this observation
might have occurred in response to precompetition
weight loss is not exactly known. It has been sug-
gested that bone turnover is always initiated by the
activation of osteoclasts eroding a mineralized sur-
face. An initial phase of bone resorption is followed
by a more prolonged phase of bone formation me-
diated by osteoblasts. The absence of a significant
acute response of serum osteocalcin in female ju-
doists to the relatively short weight reduction period
(1 week) was in accordance with the fact that osteo-
calcitonin is involved in the late phase of matrix mineralisation (Proteau, Pelle, et al., 2006). However, the authors did not rule out the possibility that the slight increase in the measured serum osteocalcin occurring 3 weeks after the weight loss episode in female judoists might be the reflection of an overall increase in bone turnover triggered by weight loss (Proteau, Pelle, et al., 2006). In support to this notion, increases in osteocalcin in response to weight loss have been reported (Ricci et al., 2001). In addition, an uncoupling index was calculated from the measured C-terminal telopeptide of type I collagen and osteocalcin values to assess the relative balance of the formation and resorption processes of bone remodelling (Proteau, Pelle, et al., 2006). The negative value of the uncoupling index as a result of precompetition weight loss indicated that the rates of bone resorption exceeded the rates of bone formation and established a bone resorptive state in female judoists, while weight regain, by decreasing bone resorption, restored a positive balance in favour of bone formation (Proteau, Pelle, et al., 2006). Thus, calculation of the uncoupling index enables a qualitative appreciation of the changes in the bone metabolic state in female athletes.

There is some evidence to suggest that high-impact loading activities have the potential to override certain adverse environmental influences on bone (Misra, 2008; Proteau, Pelle, et al., 2006). A study with amenorrheic gymnasts showed that high-impact loading in artistic gymnastics participation had a greater osteogenic effect than the increased resorption induced by amenorrhea (Robinson et al., 1995), while these benefits were not seen in endurance activities involving lower strain magnitudes (Brahm, Strom, Piehl-Aulin, Mallmin, & Ljunghall, 1997). Indeed, mechanical loading has been demonstrated to stimulate proliferation, differentiation and maturation of precursor cells in the osteoblast lineage and increase the number of mature osteoblasts in bone (Chow, Jagger, & Chambers, 1993). For example, judo has been thought to represent a sport discipline, where weight-bearing, high-magnitude, high-impact, high-velocity and highly varied physical loading characteristics cause the biochemical strains thought to have the greatest effect on bone formation in female athletes (Proteau, Pelle, et al., 2006). It has also been reported that urinary deoxypyridinoline (a bone resorption marker) values increase with intense training sessions in female athletes (Chen & Yang, 2004). Conversely, significantly lower levels for both a bone formation marker (C-terminal propeptide of type I procollagen) and a bone resorption marker (cross-linked N-telopeptide of type I collagen) were found in adolescent female athletes with amenorrhea compared with the untrained controls, whereas the levels in eumenorrheic athletes were somewhere in between (Misra, 2008). Taken together, these results demonstrate a state of reduced bone turnover in athletes with amenorrhea and most likely reflect the underlying state of negative energy balance.

**Sex hormones**

Low estrogen levels together with low calcium and protein intake combined with late menarche could lead to an increased incidence of spontaneous bone stress fractures and the development of premature osteoporosis (Nichols, Bonnick, & Sanborn, 2000). Because estrogen suppresses bone turnover, decreased estrogen levels result in bone turnover with a greater increase in bone resorption than bone formation in female athletes (Eastell et al., 1993). On the other hand, the primary goal of different exercise programmes to decrease bone loss should be the elevation of circulating estrogen levels (Burrows & Bird, 2000). Zaman, Cheng, Jessop, White, and Lanyon (2000) demonstrated that the adaptive response of bone cells to mechanical stress involves the estrogen receptor; blocking the estrogen receptor impairs the bone formation response to mechanical stress. In addition, estradiol has the strongest intracellular effect among estrogens and has a role in the prevention of bone loss, reduction of induced gain of body mass and elevation of locomotor activity after an ovariectomy (Hertrampf et al., 2007). Clegg, Brown, Woods, and Benoit (2006) suggested that estrogen acts within the brain to increase leptin sensitivity, decrease insulin sensitivity and favour subcutaneous fatty tissue over visceral fat. All these factors help to protect BMD in young females. Furthermore, it has also been found that leptin secretion can be stimulated in women by the administration of estradiol together with progesterone (Messinis et al., 2001).

In our recent study, estradiol was not related to measured BMD values in strength-trained (weightlifters and sport aerobics trainers), endurance-trained (swimmers, cross-country skiers and long distance runners), normal-weight sedentary and/or overweight sedentary young women (Sööt, Jürimäe, T., & Jürimäe, J., 2006), which is in agreement with other studies (Bemben, D.A., Buchanan, & Bemben, 2004). Progesterone correlated with BMD at the femoral neck area only in endurance-trained females (Sööt et al., 2006). It was concluded by Kaga et al. (2004) that in female long distance runners intense training may be beneficial for the cortical bone status by increasing the muscle strength but the abnormal sex steroid environment may have a lesser effect on bone metabolism. In addition, some studies that have investigated the efficacy of combined estrogen and progesterone treatment for the protection of bone mass in young physically active females with amenorrhea have shown no beneficial effect (Munoz et al., 2002), while others have reported an improvement (Hergenroeder et al., 1997).
or even a decrease (Hartard et al., 2004). Thus, the role of estrogen replacement in athletes with amenorrhea remains to be determined. However, the participants of both athletic groups in our study (endurance-and strength-trained) were not very slim and they all had a regular menstrual cycle (Sõöt et al., 2006). On the other hand, their mean body fat content was slightly lower than the proposed critical point of body fat (22%) by Frish and McArthur (1974) after regular menstruation. Therefore, estradiol concentration varied greatly within different subjects and correlated significantly with progesterone only in the normal-weight untrained group (Sõöt et al., 2006). It is well known that estrogen alone or in combination with progesterone has been demonstrated to have a protective effect against bone loss in postmenopausal women (Delaire, 1999).

As previously stated, hypoestrogenism negatively influences BMD by increasing bone resorption and decreasing bone formation markers in amenorrheic athletes (Gibson, Mitchell, Harries, & Reeve, 2004; Misra, 2008). Whereas the prevalence of amenorrhea in the general population is only 2-5% in young adult women, this can be as high as 66% in certain sports events (Loucks & Horvath, 1985; Misra, 2008). In addition to the type of physical activity, the risk of amenorrhea depends on the intensity and duration of physical activity (Misra, 2008). Many investigations have found that prolonged amenorrhea in athletes is associated with a reduction in BMD, particularly in the lumbar spine (Drinkwater, Bruemner, & Chesnut, 1990; Gibson et al., 2004). However, as exercise is an osteogenic stimulus in itself, it is possible that some bone loss due to amenorrhea may be offset in areas of high mechanical stimulus. For example, BMD at the lumbar spine in amenorrheic runners was not as low as in amenorrheic runners (Wolman et al., 1990) suggesting that running may partially counteract the reduction in BMD, presumably by the muscular strains placed on the spine by this form of exercise (Gibson et al., 2004). It has also been suggested that running may afford some protection at the proximal femur BMD in hypoestrogenic runners (Drinkwater et al., 1990; Gibson et al., 2004). It has been proposed that the duration of amenorrhea is an important factor for the development of the lumbar spine BMD (Gibson et al., 2004). This would suggest that in the spine the longer the skeleton is imposed to normal sex hormone levels after menarche, the more BMD is increased towards its peak adult value and the less the absolute value of BMD is reduced below the anticipated peak BMD by prolonged amenorrhea subsequently (Gibson et al., 2004). Accordingly, if this is true, then it will be even more important to monitor the training load and protect young athletes from amenorrhea in the first years after menarche.

Growth hormone-insulin-like growth factor axis

Rising levels of estrogen in early puberty are followed closely by rising levels of the growth hormone (GH) and IGF-I, both of which are important bone trophic hormones and important for pubertal bone modelling (Misra, 2008). It has to be taken into account that BMD in adolescent female athletes is dependent on multiple factors and physical activity per se is not always protective for bone (Misra, 2008). Some of the factors that impact BMD include the nature of the sport discipline, the extent of energy deprivation, the changes in body composition and also the levels of IGF-I (Misra, 2008). Accordingly, all these factors should be considered in determining the possible risk for low BMD and the hypoestrogenic state in female adolescent athletes.

IGF-I is involved in many functions, including the regulation of energy metabolism (Gomez et al., 2003) and playing a role in the reproductive axis (Kaaks et al., 2003). It is also known that higher circulating IGF-I concentrations are associated with greater BMD values in women, as IGF-I has been linked to the process of bone acquisition (Rosen, 2004). In contrast, the combined effects of chronic hyperglycaemia, insulin deficiency and low IGF-I concentration may reduce osteoblast activity, leading in turn to a decrease in bone formation (Thrailkill, Lumpkin Jr., Bunn, Kemp, & Fowlkes, 2005). Interestingly, IGF-I was significantly correlated with the femoral neck BMD in the untrained normal-weight group and with the distal radius BMD in the untrained overweight women, but no such relationship was seen in the strength-trained and/or endurance-trained women (Sõöt et al., 2006), which is in agreement with other studies (Seck et al., 1999). It appears that the relationship between IGF-I and BMD in young female athletes with optimal BMD levels and a regular menstrual cycle is not very strong. Interestingly, the relationship is high in healthy untrained women younger than 35 years of age, i.e. during the peak period of bone mass density (Ravn, Overgaard, Spencer, & Christiansen, 1995). However, there is also a strong relationship between the magnitude of reduction of IGF-I concentration and markers of bone formation under the conditions of energy restriction in endurance runners (Zanker & Swane, 2000). Taken together, this would suggest that a certain level of circulating IGF-I is needed in the development and/or maintenance of BMD levels, while the relationship is not so well determined under the presence of high energy expenditure in female athletes. In addition, the relationship between IGF-I and estradiol concentrations in strength-trained and endurance-trained women was not significant (Sõöt et al., 2006). This was also surprising because both parameters are known to influence BMD in young
females and on the other hand, estradiol is known to potentiate IGF-I actions (Dupont, Karas, & Leroith, 2000). Thus, it is possible that the anabolic effect of IGF-I on bone may require estradiol. However, the mean estradiol concentrations in our studied female athlete groups were on the lowest acceptable level which is suggested as being optimal for preventing postmenopausal bone loss (Reginster et al., 1992). Further studies are needed to establish whether the lack of IGF-I anabolic effects on BMD in young female athletes is really dependent on the estradiol availability. In support to our findings, lower levels of IGF-I have been found in adolescent athletes with amenorrhea in comparison with the sedentary controls (Misra, 2008). The occurrence of amenorrhea in some but not all athletes has been attributed to the state of energy balance, and an inability to balance the increased energy expenditure with the increased and adequate energy intake (Misra, 2008). The decreased levels of circulating IGF-I concentrations and decreased effect of IGF-I on BMD could be the reason for the inadequate energy balance in amenorrheic female athletes.

**Inflammatory markers**

Food restriction and energy deficiency are thought to have effects on BMD that are independent of the effects of estrogen deficiency (De Souza & Williams, 2005; Misra, 2008). It is possible that the effects of energy deficiency are related to alterations in body composition including muscle mass, an important determinant of BMD, and to nutritionally regulated hormones with known effects on bone metabolism in female athletes (Misra, 2008). A particular focus of recent research has been on the impact of the peripheral signals of energy balance, such as leptin and ghrelin (Jürimäe, J. et al., 2007), which have been associated with appetite-regulating responses at the hypothalamic and pituitary levels (Nakazato et al., 2001). Leptin is a product of the LEP gene, mainly secreted by the adipose tissue and acts directly on the hypothalamus, where it regulates a large number of molecules that are involved in energy homeostasis (Popovic & Duntas, 2005). Ghrelin, a peptide secreted by the endocrine cells in the gastrointestinal tract, transfers information from the stomach to the hypothalamus and influences the GH release in response to changes in energy homeostasis (Popovic & Duntas, 2005).

It has been found that female adolescent athletes have higher fat-free mass (FFM) than girls with anorexia nervosa and the controls (Iacopino et al., 2003), while other studies have observed marked reductions in fat mass (FM), without significant differences in FFM, in amenorrheic adolescent endurance athletes compared with eumenorrheic athletes and the sedentary controls (Misra, 2008). Furthermore, positive relationships have been found of measured BMD values with chronological and bone age, height, body mass, FM, FFM, age at onset of training, and the negative relationships with the duration and intensity of training (Markou et al., 2004; Misra, 2008). These relationships between BMD and body composition values may be mediated by leptin. Leptin strongly correlates with FM, but the relationship of leptin with BMD still remains controversial (Jürimäe, J. & Jürimäe, T., 2006). In our study, leptin was strongly related to the measured BMD values in physically active premenopausal women (Jürimäe, J. & Jürimäe, T., 2006). However, by adjusting the data for FM values, the correlation between leptin and BMD values was lost, which indicates that there is no influence of leptin on BMD independent of adiposity (Jürimäe, J. & Jürimäe, T., 2006). In contrast, a positive effect of leptin on BMD of the growing skeleton has been observed (Garnett et al., 2004). Furthermore, Garnett et al. (2004) were the first to report the FM-independent effect of leptin concentration on the lumbar spine BMD in healthy prepubertal children. In another study, Iwamoto et al. (2000) found that leptin did not play an important role in the overall bone metabolism and only influenced regional BMD in premenopausal women. Taken together, these results suggest that leptin may have a role in bone growth and development, but its role in mature bone is not fully understood.

The results of our recent study demonstrated that strength-trained female athletes and overweight untrained females were found not to have any relationships between the plasma leptin concentrations and different BMD values, while in endurance-trained female athletes and normal-weight untrained females, this relationship was significant only in the lumbar spine BMD (Sööt, Jürimäe, T., & Jürimäe, J., 2007). However, when controlled for FM, these relationships were not significant. This demonstrates that BMD is controlled by leptin only via body FM also in female athletes. Therefore, circulating leptin concentration was related to the lumbar spine BMD at the site that is a load-bearing one in endurance-trained female athletes, whose body fat percent was relatively low (Sööt et al., 2007). This may suggest that weight-bearing exercises are more important determinants of BMD than body composition values in female athletes. In accordance with this, Courteix et al. (2007) found that hypoleptinemia induced by intensive and stressing physical training did not affect the bone health of adolescent elite rhythmic gymnasts.

A recent study by Proteau, Benhamou, and Courteix (2006) examined the relationship between the circulating leptin concentration with bone biochemical markers and body composition in female judoists during stable body mass, in response to body mass reduction and also to body mass regain. The negative association between the C-terminal...
telopeptide of type I collagen (a marker of bone resorption) value and the leptin levels observed at baseline (stable body mass) was further confirmed by the biochemical changes occurring in responses to body mass loss and body mass regain. Specifically, the decrease in the leptin concentration was strongly related to the increase in bone resorption marker occurring in response to body mass loss, while the postcompetition rise in leptin concentration was associated with a concomitant decrease in bone resorption in female judoists (Proteau, Benhamou, et al., 2006). It is interesting to note that in this study, the role of leptin in the regulation of bone resorption appeared to be stronger than other potential candidates such as cortisol and insulin that did not yield any association with changes in the bone resorption marker in female judoists (Proteau, Benhamou, et al., 2006). Cortisol is known to have a catabolic effect on bone (Misra, 2008), while insulin is thought to act as an anabolic agent on bone (Thrailkill et al., 2005). For example, a condition of increased bone resorption is consistently accompanied by increased cortisol concentrations and decreased insulinemia in anorectic females (Proteau, Benhamou, et al., 2006). Indeed, the increased bone resorption found in female judoists after body mass loss was accompanied by a concomitant elevation in cortisol and a reduction in insulin concentrations. However, the absence of a significant relationship suggests that neither cortisol nor insulin played a direct role in increasing bone resorption. In contrast, osteocalcin (a marker of bone formation) remained unaffected by body mass reduction and following regain in female judoists (Proteau, Benhamou, et al., 2006). Taken together, these findings demonstrate that leptin is involved in the regulation of bone metabolism in female athletes.

Misra et al. (2005) demonstrated that ghrelin secretion predicted BMD independent of body composition, GH-IGF-I axis and/or estradiol in healthy adolescent girls. In contrast, ghrelin and leptin did not predict BMD in adolescent athletes with amenorrhea (Misra, 2008). Therefore, ghrelin has been reported to have proliferative effects on osteoblasts in cell culture (Maccarinelli et al., 2005). It appears that ghrelin may have an influence on bone metabolism in healthy females. However, decreased FM and low leptin concentrations have been implicated as a cause of amenorrhea and administration of recombinant human leptin to young adult women with amenorrhea has been reported to be associated with the resumption of ovulatory cycles, in at least some women (Misra, 2008). In addition, high ghrelin and low leptin levels that have been found in exercising amenorrheic versus eumenorrheic females suggest that higher ghrelin and lower leptin levels in some athletes may also contribute to hypoestrogenism (De Souza et al., 2004; Misra, 2008). We have recently demonstrated significantly higher ghrelin concentrations in adolescent female swimmers compared to the matched healthy untrained controls (Jürimäe, J., et al., 2007). This also suggests that chronic exposure to high energy expenditure in adolescent athletes may contribute to a high ghrelin concentration in these adolescent athletes. However, it could be speculated that the increase in estradiol levels at the beginning of puberty stimulates IGF-I secretion (Kanbur-Oksuz, Derman, & Kink, 2004) and, thus, via negative feedback, IGF-I may suppress ghrelin concentration (Jürimäe, J. et al., 2007). Estrogen has an important effect on bone mass acquisition in adolescence, and prolonged hypoestrogenism during this period could have serious implications for peak bone mass in adolescent female athletes (Misra, 2008). For example, Misra et al. (2005) speculated that high levels of ghrelin have differing effects on the different receptors mediating ghrelin effects and very high ghrelin levels may not stimulate or even indirectly decrease the osteoblast proliferation.

Conclusions and future research suggestions

To conclude, the increased participation of young female athletes in competitive sport in recent years, especially when associated with inadequate caloric intake, exposes young female athletes to several health risks such as menstrual irregularities and reproductive dysfunction. This in turn has a negative effect on BMD development in these athletes. The association of low BMD with amenorrhea in female athletes highlights the importance of assessing BMD, particularly at the site of the lumbar spine, in this specific population. However, as DXA measurement of BMD represents only a static assessment of bone health, a more dynamic nature of the bone could be obtained by measuring the biochemical markers of bone formation and resorption in blood and/or urine. To date, many studies have been performed to measure BMD using DXA in female athletes of different sport disciplines but only very few have also measured the bone turnover markers in blood and/or urine. In addition, an effort should be made to find objective hormonal parameters to quantify the balance between the actual sport training load and the tolerance of this training load by young female athletes. It has to be taken into account that when heavy training starts at a very young age, there is exposure to higher risk for developing the female athletic triad. The female athletic triad is characterised by late menarche, restrained eating behaviour and increased rate of stress fractures. For this reason, young athletes should be monitored at short intervals to understand better the influence of a high training load on the different hormonal markers that are responsible for the overall growth, including bone development, and energy homeostasis in these young athletes.
Which adult female athletes should be monitored more closely for the assessment of BMD depends on the nature of the sport discipline, duration of possible amenorrhea, extent of energy deprivation and whether or not disordered eating behaviours exist (Misra, 2008). For example, long distance runners with a prolonged duration of amenorrhea who have a history of disordered eating are at high risk for low BMD, whereas athletes representing high-impact sport disciplines such as volleyball and basketball players appear to be relatively protected. In addition to the assessment of BMD on a DXA scan, bone turnover and different hormonal parameters should be measured to understand better the mechanism of bone development. Specifically, further investigations are necessary to question the possible existence of the certain threshold for peripheral markers of energy expenditure, such as leptin and ghrelin, which may initiate the decrease in bone resorption.

References


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zitometrije (DXA - dvoenergetska apsorpciometrija biti i pod utjecajem dnevnih varijacija), mnogo bolje čini za zasebna područja skeleta, a također mogu markeri imaju određena ograničenja (nisu specifični BMD-a u medicinskom nadzoru sportašica. Iako ti gradnje predstavljaju značajan dodatak korištenju 2008). Korištenje različitih markera koštane pregradnje, dok bi snižena razina estrogena kod sportašica rezultira koštanom pregradnjom s većim porastom resorpcije kosti u odnosu na stvaranje kosti (Eastell et al., 1993). Zaman i suradnici (2000) su pokazali da adaptacijski odgovor koštanih stanica na mehanički stres uključuje estrogenski receptor. Stoviše, estradiol ima najjači unutarstanični učinak među estrogenim hormonima te ima ulogu u prevenciji gubitka koštanog tkiva (Hertrampf et al., 2007). Clegg i sur. (2006) su sugerirali da estrogen djeluje na mozak u smislu povećanja osjetljivosti na leptin, smanjenja inzulinske osjetljivosti i favoriziranja potkožne u odnosu na visceralu rasprostiranje masnog tkiva. Sve su to čimbenici koji pomažu očuvanju BMD-a kod mladih žena. Kao što je već spomenuto, hipoestrogenizam negativno utječe na BMD povećanjem resorpcijskih i smanjenjem formacijskih markera koštane pregradnje kod amenoroičnih sportašica (Gibson et al., 2004; Misra, 2008). Dok prevale nica amennoreje kod odrašlih mladih žena u općoj populaciji iznosi tek 2-3%, kod sportašica određenih sportova učestalost te pojave može narasti i do 66% (Loucks & Horvath, 1985; Misra, 2008). Osim o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenoreje ovisi o vrsti tjelesne aktivnosti, rizik od amenor...
procesom izgradnje kosti (Rosen, 2004). Ukupno gledano, to bi sugeralo da je određena razina cir-
kulirajućeg IGF-I potrebna za razvoj i/ili održava-
je razine BMD, no taj odnos još nije dovoljno do-
bro utvrđen u uvjetima visoke energetske potrošnje kod sportašica.

Proupalni markeri

Smatra se da smanjen unos hrane i energetski
nedostatak imaju učinke na BMD koji djeluju neovi-
sno o estrogenskoj deficijenciji (De Souza & Willi-
ams, 2005; Misra, 2008). Osobito žarište recentnih
istraživanja postao je utjecaj perifernih signala ener-
getske ravnoteže, poput leptina i grelina (Jürimäe
et al., 2007), koji su povezani s reakcijama koje reg-
uliraju apetit na hipotalamičkoj i hipofiznoj razini
(Nakazato et al., 2001). Leptin je produkt LEP gena,
pretežno ga izlučuje masno tkivo, a djeluje izravno
na hipotalamus (Popovic & Duntas, 2005). Grelin,
peptid koji izlučuju endokrine stanice u gastroin-
testinalnom sustavu, prenosi informacije iz želuca
u hipotalamus i utječe na lučenje GH kao odgovor
na promjene u energetskoj homeostazi (Popovic &
Duntas, 2005).

Leptin visoko korelira s masnom masom tije-
la, dok njegov odnos s BMD još uvijek ostaje kon-
troverzno pitanje (Jürimäe & Jürimäe, 2006). Za
razliku od toga, uočen je pozitivan učinak leptina
na BMD skeleta u rastu i razvoju (Garnett et al.,
2004). Leptin možda ima ulogu u rastu i razvoju
kostiju, no njegova uloga u zreloj kosti nije sasvim
razjašnjena.

Zaka

nje kod mladih sportašica, sindroma koji karakteri-
ziraju kasni nastup prve menstruacije, poremećaj
(smanjen unos) prehrane i povećana učestalost
prijeloma zamora. Zbog toga je nužno redovito
praćenje mladih sportašica u kratkim vremenskim
intervalima, da bi se bolje razumio utjecaj visokog
trenažnog opterećenja na različite hormonske mar-
kere odgovorne za opći rast, uključujući koštani ra-
zvoj i energetski homeostazu.