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INFLUENCE OF PHYSICAL ACTIVITY ON LINEAR GROWTH IN CHILDREN AND ADOLESCENTS

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ABSTRACT

Linear growth is the result of bone elongation in children and adolescents mediated by processes of endochondral ossification and maturation of bone tissue. Physical activity (PA) importantly influences both processes through systemic and local effects, mediated by growth hormone, insulin-like factor I, sex hormones, thyroid hormones, glucocorticoid hormones and various cytokines with endo-, para- and autocrine function, secreted by adipose tissue (adipokines) or muscles (myokines). It is important to promote a physically active lifestyle in early childhood as it tends to persist into adulthood together with favorable body composition. From the safety point-of-view, recent data suggests that PA does not negatively influence linear growth regardless of its duration or intensity, as long as chronic negative energy balance is prevented by sufficient energy intake.

The aim of this review is to describe current scientific knowledge on the mechanisms by which PA could influence linear growth, and present recent studies analyzing its possible effects.

Keywords: *linear growth, physical activity, energy balance, puberty, child*

VPLIV TELESNE DEJAVNOSTI NA LINEARNO RAST OTROK IN MLADOSTNIKOV

IZVLEČEK

Linearna rast je posledica daljšanja dolgih kosti pri otrocih in mladostnikih zaradi procesov endohondralne osifikacije in dozorevanja kosti. Telesna aktivnost ima pomembne učinke na oba procesa preko sistemskih in lokalnih vplivov, posredovanih s strani rastnega hormona, inzulinu podobnega rastnega faktorja 1, spolnih hormonov, ščitničnega hormona, glukokortikoidov ter številnih citokinov z endo, para in avtokrino funkcijo, ki se izločajo iz maščobnega tkiva (adipokini) in mišic (miokini). Nedavno pridobljeni podatki raziskav kažejo na to, da telesna aktivnost ne vpliva negativno na linearno rast, ne glede na njeno trajanje ali intenzivnost, če dolgoročno preprečimo negativno energijsko bilanco z zadostnim kaloričnim vnosom. Telesno aktivnost v otroštvu je pomembno spodbujati tudi z dolgoročnega zdravstvenega vidika, saj se vzorci aktivnega življenjskega sloga, skupaj z ugodno telesno sestavo, prenašajo iz otroštva v odraslo dobo.

Namen prispevka je podati trenutne znanstvene podatke o mehanizmih, preko katerih bi telesna aktivnost lahko vplivala na linearno rast.

Ključne besede: *rast, telesna aktivnost, energijska bilanca, puberteta, otrok*

INTRODUCTION

Basic principles of growth

The linear growth of a child results from bone elongation, which is the primary result of a process called endochondral ossification at the growth plate of long bones, short tubular bones of hands and feet and the vertebrae. It is a regulated physiological process, where activation of chondrocytes is followed by their proliferation. Newly formed chondrocytes are positioned on top of their predecessors arrayed in columns, which is crucial for bone elongation. At the edge of the proliferative zone closest to the metaphysis, the process of chondrocyte hypertrophy follows. Hypertrophic chondrocytes excrete extracellular matrix and attract osteoclasts, osteoblast and formation of new vessels, which remodel newly formed cartilage into bone. The growth velocity depends on the velocity of chondrocyte proliferation and their ability to hypertrophy, which is determined by an intrinsic mechanism within the growth plate (Jee & Baron, 2016).

The highest growth velocity is observed prenatally and declines rapidly after birth as a result of a programmed process intrinsic to the growth plate cartilage called senescence, which is an essential process for bone development. Senescence leads to bone maturation and simultaneously to growth cessation (Nilsson & Barron, 2004). The process is influenced by many, especially local, mediators. Their expression depends on systemic mediators such as hormones or inflammatory cytokines. Consequently, malnutrition or a chronic inflammatory state causes not only a decline in linear growth but slows down the growth plate senescence as well. When growth-inhibiting conditions are resolved, the acceleration of growth rate is observed, resulting in catch-up growth. Catch-up growth is not the result of systemic hormonal changes (e.g., higher levels of circulating growth hormone) but accelerated senescence in the growth plate (Forcinito et al., 2011).

Endocrine regulation of growth

Growth hormone (GH) and insulin-like growth factor-1 (IGF-1) are strong endocrine stimulators of growth. Defects in their production lead to growth impairment and decreased adult height, which can be prevented with adequate substitution therapy. GH's major effector site is the liver, where it stimulates the production of IGF-1. Additionally, in small part, it also has a direct effect on the growth plate, where it stimulates chondrocyte proliferation and local IGF-1 production. IGF-1 derived from the liver as well as from the growth plate, stimulates longitudinal growth inciting chondrocyte proliferation, hypertrophy and their secretory function (Nilsson, Marino, De Luca, Phillip, & Baron, 2005). During puberty, estrogen promotes longitudinal growth through promoting effects of the GH – IGF-1 axis. At the same time, it also stimulates growth plate maturation directly through receptors ER-α and

ER-β, expressed in all zones of growth plates, decreasing proliferative capacity of chondrocytes in the process of senescence (Lui, Garrison, & Baron, 2015; Weise et al., 2001). Other hormones also play an important role in longitudinal growth, with thyroid hormones, androgens and leptin having a stimulatory effect. Excessive exposure to glucocorticoids, on the other hand, has an inhibitory effect on growth. Glucocorticoids in supraphysiological levels affect growth directly at the level of the growth plate, decreasing chondrocyte proliferation as well as their hypertrophy and indirectly cause downregulation of growth hormone and IGF-1 receptor expression. Additionally, they increase the circulating levels of IGFBP-1, which could potentially affect the circulating levels of free IGF-1 (Jee & Baron, 2016, Gat-Yablonski & Phillip, 2015; Nilsson et al., 2005).

Endocrine regulation of longitudinal bone growth is governed by a complex network of endocrine signals. Most of these hormones regulate growth plate directly by acting on growth plate chondrocytes and indirectly by modulating other endocrine signals in the network. E.g., during puberty, increased estrogen secretion increases GH secretion and stimulates the process of growth and senescence at the level of the growth plate, causing growth acceleration in the beginning and later growth cessation, when the number of chondrocyte progenitor cells decreases (Nilsson et al., 2005).

Calcium and vitamin D

In addition to caloric intake, adequate intake of calcium and vitamin D should be ensured for optimal growth plate development (Lui, Garrison, & Baron, 2015; Nilsson et al., 2005). Calcium is the main mineral component of the skeleton, and for skeletal growth a sufficient calcium supply is therefore essential. Accordingly, nutritional factors (like food allergies) that affect calcium metabolism will also be of importance for adult height (Christie, Hine, Parker, & Burks, 2002). Adequate calcium intake is known to increase peak bone mass in early adulthood; however, Welten et al. (1994) observed in a 15-year-long longitudinal study that the only two significant predictors for achieving the highest peak bone mass in early adulthood were regular weight bearing exercise and normal age-related body weight in adolescence. Calcium intake did not appear to predict bone density in either sex.

The main regulator of calcium metabolism is vitamin D, which regulates the process of endochondral ossification by positively affecting chondrocyte proliferation, hypertrophy and differentiation of osteoblasts. The effect of vitamin D on the skeleton is not only demonstrated by severe deficiency leading to rickets (which is also associated with short stature). In fetal growth, maternal pre-natal vitamin D deficiency has been associated negatively with bone mineralization, lower birth weight and an increased risk of neonates born small for gestational age (Eckhardt, Gernand, Roth, & Bodnar 2014; Viljakainen et al., 2010). The active form of vitamin D binds with the nuclear receptor (VDR), which is found throughout the body, including in the growth plates. Different single nucleotide polymorphisms in the VDR gene relate to the

adult height difference up to 2 cm. Furthermore, positive association between serum vitamin D level and height in young adults has also been reported (Jorde, Svartberg, Joakimsen, & Grimnes, 2012; Kremer, Campbell, Reinhardt, & Gilsanz, 2009).

Physical activity

Physical activity (PA) is defined as any activity of the body produced by skeletal muscles that requires energy expenditure. It is considered as a type of structured, organized, and previously planned exercise with the aim of improving or maintaining physical condition. There are different forms and patterns of PA; its intensity is usually divided into light (LPA), moderate (MPA), moderate to vigorous (MVPA) and vigorous intensity activity (VPA). Its positive effects on cardiometabolic biomarkers, physical fitness, bone health, motor skill development, psychosocial and cognitive health in children and adolescents are already well known and have recently been evaluated in an extensive review by Poitras et al. (2016). In general, higher intensity, frequency and longer duration of PA had a stronger relationship with the positive effects than lower intensity PA. All patterns of activity (sporadic, bouts, continuous) were found beneficial (Poitras et al., 2016). By current guidelines 60 minutes per day of MVPA for children and youth is recommended for promotion of health and disease prevention (WHO, 2010). Furthermore, a physically active lifestyle developed in early childhood, together with body composition, tends to persist along the entire life course (Fraser et al., 2017).

Recent data suggests that PA does not negatively influence linear growth regardless of its form, pattern, intensity and duration (Alves & Alves, 2019), if chronic negative energy balance is prevented by sufficient energy intake. However, less is known about the exact effect of PA at the level of epiphyseal growth plates, altering their growth potential, through systemic and local endocrine mechanisms. These effects are more pronounced in children and adolescents engaged in sports activities, who are usually more physically active than the recommended guidelines. It is thought that PA has a protective role on growth plates in this population; however, if not carefully planned, it could have direct negative consequences on growth plates through injury or indirectly through influencing pubertal development, nutritional levels and body composition (Mirtz, Chandler, & Eyers, 2011; Gat-Yablonski & Phillip, 2015).

The aim of this review is to describe current scientific knowledge on the mechanisms by which PA could influence linear growth and present recent studies analyzing its possible effects.

MECHANISMS THROUGH WHICH PHYSICAL ACTIVITY COULD AFFECT THE GROWTH PLATE

Growth hormone - IGF-1 axis

Processes of endochondral ossification and senescence at the growth plate are the main mechanisms being discussed in relation to the effect that PA could have on growth. Several interconnected factors influence the growth, with the effect of hormones being the most well studied. PA stimulates secretion of GH from the pituitary gland, which directly - at the level of the growth plate - and indirectly - in the liver - stimulates IGF-1 production. However, the reports about increased circulating total and free IGF-1 (not bound to IGF-binding proteins - IGFBP) levels during and after exercise are inconsistent (Wang et al., 2011; Frystyk, 2010). The effect of these hormones was further evaluated in correlation to IGFBP dynamics during exercise because most of IGF-1 is bound to IGFBPs in the circulation. IGFBPs prolong the half-life of IGF-I and act as autocrine and/or paracrine regulators of its biological activities, potentially altering the availability of free IGF-1, without changing total IGF-1. An increase in IGFBP-1 levels is seen during prolonged exercise, whereas reports about IGFBP-3 are inconsistent. IGFBP dynamics in the circulation are also closely related to changes in glucose and insulin metabolism, glucocorticoid and growth hormone levels. Despite their changed levels in the circulation connected with PA, the results of studies on the effect on the circulating IGF-1 levels remain inconclusive (Frystyk, 2010).

As previously mentioned, GH does not only stimulate hepatic, but also local IGF-1 production, which increases IGF-1 concentration at the growth plate level as well as in muscles (Wang et al., 2011; Desvigne, Barthelemy, Frere, Gay-Montchamp, & Costes, 2005). Studies suggest that locally/peripherally produced IGF-1 is the main determinant of somatic growth and the liver is responsible for circulating IGF-1 levels, which control pituitary GH secretion (Domene et al., 2007; LeRoith, Bondy, Yakar, Liu, & Butler, 2001). Therefore, in the future, tissue-specific levels of IGF should be analyzed to assess the effect of PA on the growth plate.

Puberty and energy balance

Pubertal development and its growth spurt can be significantly affected by PA. As discussed previously, sex hormones in puberty, especially estrogen in both sexes, have an important role in mediating the effects of GH-IGF-1, not only at the level of secretion but also at the level of GH action. Estrogen enhances growth through augmentation of GH-dependent chondrocyte proliferation at the growth plate. At the same time, it affects growth plates senescence by reducing the rate of chondrocyte proliferation, growth plate height, number of proliferative chondrocytes, number of hypertrophic chondrocytes, size of terminal hypertrophic chondrocytes and column density, leading to epiphysial fusion and growth cessation (Weise et al., 2001). PA is

associated with increased energy consumption and in conjunction with insufficient energy intake results in negative energy balance. This may lead to a decrease in the proportion of adipose tissue and levels of adipokine leptin, which, especially if rapid or marked, further leads to a syndrome called relative energy deficiency in sports (RED-S) (Mountjoy et al., 2018). Periods of rapid growth, such as fetal life and pubertal growth spurt require a certain level of leptin as one of several metabolic factors to allow pubertal maturation to proceed and later reproduction to occur. Leptin by itself has also been shown to have a direct positive effect on chondrocyte proliferation and differentiation at the level of the growth plate, increasing the expression of IGF-1 receptors locally, and additionally stimulating GH secretion (Maqsood et al., 2007; Gat-Yablonski & Phillip, 2015).

RED-S is characterized by hormonal disorders at several levels, the most important being hypothalamic-pituitary dysfunction (Mountjoy et al., 2018). The most frequently described is decreased gonadotropin secretion (hypothalamic hypogonadism), but hormonal disorders are present at other levels. It also interferes with the function of growth factors, thyroid hormone and cortisol. Consequently, puberty in boys and girls is delayed. Directly and indirectly, hypothalamic hypogonadism decreases bone density, causes disturbances in the functioning of the immune system, hematologic complications and malfunction of the gastrointestinal system, etc. (Mountjoy et al., 2018). Long-term hypothalamic hypogonadism is also associated with decreased fertility (Joy et al., 2014). Although research was more focused on girls, it is clear today, that RED-S affects boys as well (Tenforde, Barrack, Nattiv, & Fredericson, 2016; Mountjoy et al., 2018). Young athletes, especially in sports, where slim stature is important and dietary restrictions are common, are the most susceptible group for this syndrome; e.g., ballet dancers, gymnasts, bodybuilders, long-distance runners. Because of the short- and long-term consequences of intense PA in the case of insufficient energy intake, we should take it into account when planning PA. In case of unsuccessful prevention, the consequences should be dealt with immediately. At an early stage the vast majority of these complications are reversible (Mountjoy et al., 2018; Fagerberg, 2018). So far there are no reports about linear growth retardation in RED-S; however, it has been reported consistently in various studies of male and female adolescents with severe anorexia nervosa, demonstrating partial, but not always complete, catch-up growth after recovery (Modan-Moses et al., 2012; Modan-Moses et al., 2003).

Other hormonal axis and inflammatory cytokines

PA also affects the excretion and functioning of several other circulating hormones known to be involved in the regulation of the process of endochondral ossification and senescence. Exercise decreases insulin secretion and increases catecholamine, glucocorticoid and androgen secretion. All these effects are measured in the blood; however, less is known about the levels and actions of these hormones at the level of the growth plate, especially in correlation with PA (Riddell, 2008).

Stressful conditions, such as acute or chronic diseases and malnutrition, increase levels of glucocorticoids and inflammatory cytokines, which are known factors for growth attenuation. As mentioned above, glucocorticoids in supraphysiological levels affect growth directly at the level of the growth plate decreasing chondrocyte proliferation and indirectly cause downregulation of the growth hormone and IGF-1 receptor expression (Jee & Baron, 2016, Gat-Yablonski & Phillip, 2015). Inflammatory cytokines, such as TGF-β, IL-1β, and IL-6, act directly on binding to their receptors in the growth plate cartilage and thereby suppress bone growth. Additionally, cytokines have an indirect effect, suppressing levels of circulating IGF-1 (Cirillo, Lazzeroni, Sartori, & Street, 2017). PA is associated with the secretion of contraction induced myokines and inflammatory mediators. For example, higher-intensity and longer-duration exercise results in increased circulating concentrations of IL-6 in humans, with greater levels of IL-6 seen in cells with lower glycogen content, and due to the energy crisis in the muscle cell during contraction (Carson, 2017). However, the effect of those mediators from active skeletal muscle on children's growth, who are engaged in professional sports and exceed the recommended time of daily PA, is unknown.

Mechanical forces on the growth plate

In growing children, growth plates are more susceptible to positive as well as negative direct mechanical effects of moving. Injuries to growth plate can occur with chronic excessive PA or acute severe injury. The highest incidence of these injuries is between 10 and 16 years of age and they can result in premature locking of the epiphyseal growth plate resulting in permanent growth cessation or limited growth. Repetitive trauma can cause the epiphyseal plate to widen (Laor, Wall, & Vu, 2006). Thus, age-appropriate intensity and duration of PA is recommended, suited to the individual's psychological and physical development. It is probably associated with a favorable inflammatory mediator profile and has a beneficial effect on health, growth, and very likely plays a protective role on the growth plate (Carson, 2017; Mirtz, Chandler, & Eyers, 2011).

On the other hand, physical inactivity is thought to have a negative effect on the growth plates. It is known that load-bearing tissue, such as articular cartilage, will atrophy in the absence of mechanical forces. One can presume that sedentarism may result in inadequate stimulation of the growth plate with a possible result of changed growth potential, however the exact effects of a lack of load bearing through a lack of physical activity on the growth plates remain unknown (Darling & Athanasiou, 2003; Mirtz, Chandler, & Eyers, 2011). The rising sedentary lifestyle has other well-known consequences, such as higher risk of obesity, higher adipose tissue proportion and lower proportion of non-fatty tissue, described in detail elsewhere (Tremblay et al., 2011; Kotnik, Fischer Posovszky, & Wabitsch, 2015; Wennberg, Gustafsson, Howard, Wennberg, & Hammarström, 2014). Oftedal et al. (2016) investigated the effect

of inactivity in patients with cerebral palsy on their height. Their results showed that an individual's gross motor capacity affects final height in addition to their gestational age at birth. Children whose gross motor function was reduced (level III or IV in the gross motor function classification system), were significantly shorter and grew slower in comparison to their peers with level I or II gross motor function capacity. They also spent more time sedentary and had lower habitual physical activity. Additionally, weight-bearing PA was shown to increase bone mineral content in patients with spastic cerebral palsy (Chad, Bailey, McKay, Zello, & Snyder, 1999).

STUDIES ON THE EFFECT OF PHYSICAL ACTIVITY ON LINEAR GROWTH

Starting with fetal growth, recent data suggests that in general, in physically active pregnant women fetal growth is not affected, regardless of the PA type and intensity. PA generally benefits women in many ways (reducing edema, constipation, anxiety, insomnia and the risk of depression) (Alves & Alves, 2019). However, Wiebe, Boulé, Chari and Davenport (2015) observed that the weight of newborns was decreased by 200-400g in women preforming VGA in the last trimester, without increasing the risk of being born small for gestational age. The current recommendation during pregnancy is for previously sedentary women performing PA of mild to moderate intensity and for previously physically active women performing PA of moderate to vigorous intensity (Gregg & Ferguson, 2017).

In preterm infants passive PA has been shown to affect linear growth. A recent systematic Cochrane review by Schulzke, Kaempfen, Trachsel, & Patole (2014) assessed 11 trials with 324 preterm infants with gestational age between 26 and 34 weeks, who underwent physical activity interventions ranging from three to eight weeks of duration. The authors concluded that there is evidence suggesting that physical activity programs positively affect linear growth, promote short-term weight gain and bone mineralization in preterm infants. Data were inadequate to allow assessment of harm or long-term effects.

In healthy preschool children, the data on the effects of PA on linear growth is scarce and does not allow any conclusions. Torun and Viteri (1994) observed that in malnourished children, 24-48 months old, recovering from protein-energy malnutrition, linear growth was more intense in those who were physically active (LPA and MPA). Both groups (inactive and active) had similar dietary intake. After 6 weeks, both groups gained an average of 1.98 kg. However, the active group grew more in length (22 ± 8 vs. 14 ± 6 mm, $p < 0.05$) and lean body mass (final creatinine-height index): 0.97 ± 0.12 vs 0.89 ± 0.09, $P < 0.05$). Other studies with healthy children did not reveal an affect on linear growth; however, they indicated PA in early life appears to shape, for instance, muscle and adipose tissue. There is a consensus that PA should be incorporated early in a child's life since body composition and patterns of PA tend to persist into adult life (Twisk, 2001; Fraser et al., 2017; Alves & Alves, 2019).

In schoolchildren PA - including strength training, VPA and practicing of different competitive sports - was not found to influence linear growth. A systematic review of 16 studies with 1008 analyzed participants, assessing the effect of strength training or resistance exercises on the linear growth in children aged 7 to 12 years, did not detect any difference in the linear growth of the children who underwent strength training and those who did not ($p = 0.46$) (Alves & Alves, 2019). Similarly, it was shown by other studies that performing competitive sport at this age does not compromise linear growth. PA at this age was associated with reduced adipose tissue, an increase in bone (reducing the risk of osteoporosis later in life) and muscle mass (Damsgaard, Bencke, Matthiesen, Petersen, & Müller, 2000; Farr, Laddu, Blew, Lee, & Going, 2013; Malina, 2006; Fuchs, Bauer, & Snow, 2001).

Similarly to the previous group, PA including VPA and practice of different competitive sports in adolescence was not found to impair linear growth, as long as negative energy balance is prevented (Georgopoulos et al., 2004, Malina et al., 2013). Additionally, Malina (2006) reported that resistance training programs in this age group were not found to influence growth. Studies indicate that PA impacts bone and muscle mass growth in this age group. Nilsson et al. (2014) showed that the practice of physical exercises in adolescence increases the cortical bone through periosteal expansion, providing a more durable bone throughout life. Especially weight-bearing exercises were found consistently connected with increased peak bone mass (Chahar, 2014). Similarly, it has been shown that muscle mass, which begins to increase with pubertal development, benefits from PA. Performing PA in adolescence contributes to a higher percentage of muscle tissue in adult life (Chahar, 2014; Iuliano-Burns, Mirwald, & Bailey, 2001; Alves & Alves, 2019).

CONCLUSIONS

Physical activity is an important component of a healthy lifestyle in children and adolescents. When planning PA we have to keep in mind possible negative influence on the linear growth - e.g., by directly affecting growth plates through injury or indirectly through influencing pubertal development, nutritional levels, and body composition. In the future research should focus more on the roles and mechanisms of local mediators (hormones and cytokines) at the level of growth plates in relation to PA. This would enable us to make a better assessments of the effect of PA on linear growth and help us determine the adequate intensity of PA, preventing possible harmful effects on growing children. Additionally, with the rising sedentary lifestyle in children and adolescents, further research on the effects of decreased PA on growth plates in this population should be performed.

REFERENCES

Alves, J. B. G., & Alves, G. V. (2019). Effects of physical activity on children's growth. Jornal de Pediatria, 95(Suppl. 1), 72-78. https://doi.org/10.1016/j.jped.2018.11.003.

Carson B. P. (2017). The potential role of contraction-induced myokines in the regulation of metabolic function for the prevention and treatment of type 2 diabetes. Frontiers in Endocrinology 8, 97. https://doi.org/10.3389/fendo.2017.00097.

Chad, K. E., Bailey, D. A., McKay, H. A., Zello, G. A., & Snyder, R. E. (1999). The effect of a weight-bearing physical activity program on bone mineral content and estimated volumetric density in children with spastic cerebral palsy. The Journal of Pediatrics, 135(1), 115–117. https://doi.org/10.1016/s0022-3476(99)70340-9.

Chahar, O. S. (2014). Physiological basis of growth and development among children and adolescents in relation to physical activity. American Journal of Sports Science and Medicine, 2(5), 17-22. https://doi.org/10.12691/ajssm-2-5A-5.

Christie, L., Hine, R. J., Parker, J. G., & Burks, W. (2002). Food allergies in children affect nutrient intake and growth. Journal of the American Dietetic Association, 102(11), 1648-1651. https://doi.org/10.1016/S0002-8223(02)90351-2.

Cirillo, F., Lazzeroni, P., Sartori, C., & Street, M. E. (2017). Inflammatory diseases and growth: effects on the GH-IGF axis and on growth plate. International Journal of Molecular Sciences, 18(9), 1878. https://doi.org/10.3390/ijms18091878.

Damsgaard, R., Bencke, J., Matthiesen, G., Petersen, J. H., & Müller, J. (2000). Is prepubertal growth adversely affected by sport? Medicine and Science in Sports and Exercise, 32(10), 1698-1703. https://doi.org/10.1097/00005768-200010000-00006.

Darling, E. M., & Athanasiou, K. A. (2003). Biomechanical strategies for articular cartilage regeneration. Annals of Biomedical Engineering, 31(9), 1114–1124. https://doi.org/10.1114/1.1603752.

Desvigne, N., Barthelemy, J. C., Frere, D., Gay-Montchamp, J. P., & Costes, F. (2005). Microdialysis of insulin-like growth factor-I in human muscle. European Journal of Applied Physiology, 94(1), 216–219. https://doi.org/10.1007/s00421-004-1292-1.

Domene, H. M., Martinez, A. S., Frystyk, J., Bengolea, S. V., Ropelato, M. G., Scaglia, P. A., ... Jasper H. G. (2007). Normal growth spurt and final height despite low levels of all forms of circulating insulin-like growth factor I in a patient with acid-labile subunit deficiency. Hormone Research, 67(5), 243–249. https://doi.org/10.1159/000098479.

Eckhardt, C. L., Gernand, A. D., Roth, D. E., & Bodnar, L. M. (2014). Maternal vitamin D status and infant anthropometry in a US multi-centre cohort study. Annals of Human Biology, 42(3), 217–224. https://doi.org/10.3109/03014460.2014.954616.

Fagerberg, P. (2018). Negative consequences of low energy availability in natural male bodybuilding: a review. International Journal of Sport Nutrition and Exercise Metabolism, 28(4), 385-402. https://doi.org/10.1123/ijsnem.2016-0332.

Farr, J. N., Laddu, D. R., Blew, R. M., Lee, V. R., & Going, S. B. (2013). Effects of physical activity and muscle quality on bone development in girls. Medicine and Science in Sports and Exercise, 45(12), 2332-2340. https://doi.org/10.1249/MSS.0b013e31829c32fe.

Forcinito, P., Andrade, A. C., Finkielstain, G. P., Baron, J., Nilsson, O., & Lui, J. C. (2011). Growth-inhibiting conditions slow growth plate senescence. Journal of Endocrinology, 208(1), 59–67. https://doi.org/10.1677/JOE-10-0302.

Fraser, B. J., Schmidt, M. D., Huynh, Q. L., Dwyer, T., Venn, A. J., & Magnussen, C. G. (2017). Tracking of muscular strength and power from youth to young adulthood: longitudinal findings from the Childhood Determinants of Adult Health Study. Journal of Science and Medicine in Sport, 20(10), 927-931. https://doi.org/10.1016/j.jsams.2017.03.021.

Frystyk, J. (2010). Exercise and the growth hormone-insulin-like growth factor axis. Medicine and Science in Sports and Exercise, 42(1), 58-66. https://doi.org/10.1249/MSS.0b013e3181b07d2d.

Fuchs, R. K., Bauer, J. J., & Snow, C. M. (2001). Jumping improves hip and lumbar spine bone mass in prepubescent children: a randomized controlled trial. Journal of Bone and Mineral Research, 16(1), 148-156. https://doi.org/10.1359/jbmr.2001.16.1.148.

Gat-Yablonski, G., & Phillip, M. (2015). Nutritionally induced catch-up growth. Nutrients, 7(1), 517–551. https://doi.org/10.3390/nu7010517.

Georgopoulos, N. A., Markou, K. B., Theodoropoulou, A., Vagenakis, G. A., Mylonas, P., & Vagenakis, A. G. (2004). Growth, pubertal development, skeletal maturation and bone mass acquisition in athletes. Hormones, 3(4), 233-243. Retrieved from http://www.hormones.gr/pdf/1116416978.pdf.

Gregg, V. H., & Ferguson, J. E. (2017). Exercise in pregnancy. Clinics in sports medicine, 36(4), 741-752. https://doi.org/10.1016/j.csm.2017.05.005.

Iuliano-Burns, S., Mirwald, R. L., & Bailey, D. A. (2001). Timing and magnitude of peak height velocity and peak tissue velocities for early, average, and late maturing boys and girls. American Journal of Human Biology, 13(1), 1–8. https://doi.org/10.1002/1520--6300(200101/02)13:1<1::AID-AJHB1000>3.0.CO;2-S.

Jee, Y. H., & Baron, J. (2016). The biology of stature. Journal of Pediatrics, 173, 32–38. https://doi.org/10.1016/j.jpeds.2016.02.068.

Jorde, R., Svartberg, J., Joakimsen, R. M., & Grimnes, G. (2012). Associations between polymorphisms related to calcium metabolism and human height: The Tromsø Study. Annals of Human Genetics, 76(3), 200–210. https://doi.org/10.1111/j.1469-1809.2012.00703.x.

Joy, E., Souza, M. J., Nattiv, A., Misra, M., Williams, N. I., Mallinson, R. J., … Sundgot, J. (2014). Female athlete triad coalition consensus statement on treatment and return to play of the female athlete triad. Current Sports Medicine Reports, 13(4), 219–232. https://doi.org/10.1249/JSR.0000000000000077.

Kotnik, P., Fischer Posovszky, P., & Wabitsch, M. (2015). Endocrine and metabolic effects of adipose tissue in children and adolescents. Slovenian Journal of Public Health, 54(2), 131–138. https://doi.org/10.1515/sjph-2015-0020.

Kremer, R., Campbell, P. P., Reinhardt, T., & Gilsanz, V. (2009). Vitamin D status and its relationship to body fat, final height, and peak bone mass in young women. Journal of Clinical Endocrinology and Metabolism, 94(1), 67–73. https://doi.org/10.1210/jc.2008-1575.

Laor, T., Wall, E. J., & Vu, L. P. (2006). Physeal widening in the knee due to stress injury in child athletes. American Journal of Roentgenology, 186(5), 1260-1264. https://doi.org/10.2214/AJR.04.1606.

LeRoith, D., Bondy, C., Yakar, S., Liu, J. L., & Butler, A. (2001). The somatomedin hypothesis: 2001. Endocrine Reviews, 22(1), 53–74. https://doi.org/10.1210/edrv.22.1.0419.

Lui, J. C., Garrison, P., & Baron, J. (2015). Regulation of body growth. Current Opinion in Pediatrics, 27(4), 502–510. https://doi.org/10.1097/MOP.0000000000000235.

Malina, R. M. (2006). Weight training in youth-growth, maturation, and safety: an evidence-based review. Clinical Journal of Sport Medicine, 16(6), 478-487. https://doi.org/10.1097/01.jsm.0000248843.31874.be.

Malina, R. M., Baxter-Jones, A. D., Armstrong, N., Beunen, G. P., Caine, D., Daly, R. M., ... & Russell, K. (2013). Role of intensive training in the growth and maturation of artistic gymnasts. Sports Medicine, 43(9), 783-802. https://doi.org/10.1007/s40279-013-0058-5.

Maqsood, A. R., Trueman, J. A., Whatmore, A. J., Westwood, M., Price, D. A., Hall, C. M., & Clayton, P. E. (2007). The relationship between nocturnal urinary leptin and gonadotrophins as children progress towards puberty. Hormone Research in Paediatrics, 68(5), 225–230. https://doi.org/10.1159/000101335.

Mirtz, T. A., Chandler, J. P., & Eyers, C. M. (2011). The effects of physical activity on the epiphyseal growth plates: a review of the literature on normal physiology and clinical implications. Journal of Clinical Medicine Research, 3(1), 1–7. https://doi.org/10.4021/jocmr477w.

Modan-Moses, D., Yaroslavsky, A., Kochavi, B., Toledano, A., Segev, S., Balawi, F., ... Stein, D. (2012). Linear growth and final height characteristics in adolescent females with anorexia nervosa. PloS one, 7(9). https://doi.org/10.1371/journal.pone.0045504.

Modan-Moses, D., Yaroslavsky, A., Novikov, I., Segev, S., Toledano, A., Miterany, E., & Stein, D. (2003). Stunting of growth as a major feature of anorexia nervosa in male adolescents. Pediatrics, 111(2), 270-276. https://doi.org/10.1542/peds.111.2.270.

Mountjoy, M., Sundgot-Borgen, J., Burke, L., Ackerman, K. E., Blauwet, C., Constantini, N., … Budgett, R. (2018). IOC consensus statement on relative energy deficiency in sport (RED-S): 2018 update. British Journal of Sports Medicine, 52(11), 687–697. https://doi.org/10.1136/bjsports-2018-099193.

Nilsson, O., & Baron, J. (2004). Fundamental limits on longitudinal bone growth: growth plate senescence and epiphyseal fusion. Trends in Endocrinology and Metabolism, 15(8), 370–374. https://doi.org/10.1016/j.tem.2004.08.004.

Nilsson, O., Marino, R., De Luca, F., Phillip, M., & Baron, J. (2005). Endocrine Regulation of the Growth Plate. Hormone Research in Paediatrics, 64(4), 157–165. https://doi.org/10.1159/000088791.

Nilsson, M., Sundh, D., Ohlsson, C., Karlsson, M., Mellstrom, D., & Lorentzon, M. (2014). Exercise during growth and young adulthood is independently associated with cortical bone size and strength in old Swedish men. Journal of Bone and Mineral Research, 29(8), 1795-1804. https://doi.org/10.1002/jbmr.2212.

Oftedal, S., Davies, P. S. W., Boyd, R. N., Stevenson, R. D., Ware, R. S., Keawutan, P., … Bell, K. L. (2016). Longitudinal growth, diet, and physical activity in young children with cerebral palsy. Pediatrics, 138(4). https://doi.org/10.1542/peds.2016-1321.

Poitras, V. J., Gray, C. E., Borghese, M. M., Carson, V., Chaput, J. P., Janssen, I., ... Sampson, M. (2016). Systematic review of the relationships between objectively measured physical activity and health indicators in school-aged children and youth. Applied Physiology, Nutrition, and Metabolism, 41(6), 197-239. https://doi.org/10.1139/apnm-2015-0663.

Riddell, M. C. (2008). The endocrine response and substrate utilization during exercise in children and adolescents. Journal of Applied Physiology, 105(2), 725–733. https://doi.org/10.1152/japplphysiol.00031.2008.

Schulzke, S. M., Kaempfen, S., Trachsel, D., & Patole, S. K. (2014). Physical activity programs for promoting bone mineralization and growth in preterm infants. Cochrane Database of Systematic Reviews, (4). https://doi.org/10.1002/14651858.CD005387.pub3.

Tenforde, A. S., Barrack, M. T., Nattiv, A., & Fredericson, M. (2016). Parallels with the Female Athlete Triad in Male Athletes. Sport Medicine, 46(2), 171–182. https://doi.org/10.1007/s40279-015-0411-y.

Torun, B., & Viteri, F. E. (1994). Influence of exercise on linear growth. European Journal of Clinical Nutrition, 48(1), 186-189. Retrieved from http://archive.unu.edu/unupress/food2/UID06E/UID06E18.HTM.

Tremblay, M. S., LeBlanc, A. G., Kho, M. E., Saunders, T. J., Larouche, R., Colley, R. C., … Gorber, S. C. (2011). Systematic review of sedentary behaviour and health indicators in school-aged children and youth. International Journal of Behavioral Nutrition and Physical Activity, 8(1), 98. https://doi.org/10.1186/1479-5868-8-98.

Twisk, J. W. (2001). Physical activity guidelines for children and adolescents: a critical review. Sports Medicine, 31(8), 617-627. https://doi.org/10.2165/00007256-200131080-00006.

Viljakainen, H. T., Saarnio, E., Hytinantti, T., Miettinen, M., Surcel, H., Makitie, O., … Lamberg-Allardt, C. (2010). Maternal vitamin D status determines bone variables in the newborn. Journal of Clinical Endocrinology & Metabolism, 95(4), 1749-1757. https://doi.org/10.1210/jc.2009-1391.

Wang, Y., Cheng, Z., Elalieh, H. Z., Nakamura, E., Nguyen, M. T., … Chang, W. (2011). IGF-1R signaling in chondrocytes modulates growth plate development by interacting with the PTHrP/Ihh pathway. Journal of Bone and Mineral Research, 26(7), 1437-1446. https://doi.org/10.1002/jbmr.359.

Weise, M., De-Levi, S., Barnes, K. M., Gafni, R. I., Abad, V., & Baron, J. (2001). Effects of estrogen on growth plate senescence and epiphyseal fusion. Proceedings of the National Academy of Sciences, 98(12), 6871-6876. https://doi.org/10.1073/pnas.121180498.

Welten, D. C., Kemper, H. C. G., Post, G. B., Van Mechelen, W., Twisk, J., Lips, P., & Teule, G. J. (1994). Weight-bearing activity during youth is a more important factor for peak bone mass than calcium intake. Journal of Bone and Mineral Research, 9(7), 1089-1096. https://doi.org/10.1002/jbmr.5650090717.

Wennberg, P., Gustafsson, P. E., Howard, B., Wennberg, M., & Hammarström, A. (2014). Television viewing over the life course and the metabolic syndrome in mid-adulthood: a longitudinal population-based study. Journal of Epidemiology & Community Health, 68(10), 928–933. http://doi.org/10.1136/jech-2013-203504.

World Health Organization. (2010). Global recommendations on physical activity for health. World Health Organization. Retrieved from https://www.who.int/dietphysicalactivity/publications/9789241599979/en/.

Wiebe, H. W., Boulé, N. G., Chari, R., & Davenport, M. H. (2015). The effect of supervised prenatal exercise on fetal growth: a meta-analysis. Obstetrics and Gynecology, 125(5), 1185-1194. https://doi.org/10.1097/AOG.0000000000000801.