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Osteoporosis Is a "Silent" Problem in Children's Sport Medicine

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Abstract: The article is devoted to one of the relevant problems of modern medicine - osteoporosis. Osteoporosis epidemiology, risk factors, diagnostic approaches, which are confirmed in domestic and foreign researches, are discussed. Particular attention is paid to the ambiguity and inconsistency of information on osteoporosis in childhood and adolescence, as well as the lack of convincing studies of this issue in children's sports medicine. The authors analyze the generally accepted approaches to the identification of risk groups for the osteoporosis development in children, the predisposing factors and the complex issues of osteoporosis diagnostics. Paper includes data on own observations of the most complex group of children and adolescents involved in sport, including professional sport. A separate section is devoted to the analysis of prescribed medications for the prevention and treatment of osteoporosis in children and young athletes. The data are presented in accordance with the official information provided by World Anti-Doping Agency (WADA, 2017).

Keywords: Children, Young Athletes, Osteoporosis, Sport Medicine

1. Introduction

Despite the fact that the problem of osteoporosis is most relevant to the high risk of bone fractures in elderly and senile patients, nowadays, worldwide data shows significant osteoporosis signs presence in athletes of all ages including juniors. As a confirmation, following diseases and clinically or socially significant conditions are often found in athletes: chronic osteoarthritis as a result of extra bone and joints trauma, immune disorders and frequent infectious diseases, the risk of impaired glucose tolerance and/or diabetes mellitus development, and others [1, 2].

Research data shows that low rate of peak bone mass, calcium intake, and vitamin D supplementation, nutritional features (including regional features), and excessive physical activity are significant factors that determine and/or predispose to osteoporosis development. These factors are often revealed in professional athletes of different ages and with different sport experience [3-5].

Osteoporosis in children is considered as a calcium-deficient disease [6]. In severe osteoporosis, bone mass is reduced to 40-50% of the age norm. Because of this, the bone become less resistant to mechanical load, so fractures can easy occur even with minimal trauma and pressure.

Osteoporosis is a multifactorial systemic metabolic disease of bones, characterized by bone mass reduction per unit volume and violation of bone microarchitecture and leading to excessive bone brittleness and high risk of fractures. According to the WHO, the global prevalence of osteoporosis is on the fourth place after cardiovascular diseases, oncological diseases and diabetes mellitus. At present, osteoporosis is called a "silent" epidemic, since it long remains asymptomatic. Osteoporosis is often diagnosed already in the presence of complications, i.e. fractures. It is found that osteoporotic fractures are registered more often than myocardial infarction, strokes and breast cancer, and almost every fifth patient with an osteoporotic fracture of the

femoral neck or spine dies within a year. In women, the number of deaths as a result of femoral neck fracture is equal to breast cancer and 4 times more than endometrial cancer [8].

Medical and social costs from osteoporosis, including economic costs for the diagnosis, treatment and rehabilitation of patients with osteoporotic fractures are very high. The annual spending only on hospitalized patients with femoral neck fractures is 300 million euros in Sweden, 600 in France and 847 in England. The severity of the osteoporosis problem is confirmed by the data of the US National Osteoporosis Foundation (NOF) – more than 9.9 million Americans have osteoporosis, and 43.1 million have a decreased bone density [8]. Osteoporosis is dangerous because it can be asymptomatic for a long time, and then it is complicated with a fracture due to minimal impact or without any trauma.

Earlier, osteoporosis was considered as an exceptionally elderly disease caused by age-related bone mass loss, but at present it is proven that the origin of the disease lie in childhood – in the period of an intensive increase in bone mass.

The individual growth program consists in achieving genetically programmed not only linear dimensions, but also mineral density of bone tissue. Along with this, there are many endogenous and exogenous factors before and after birth, which can cause deviations in the genetic development program, including bone tissue development. Therefore, various osteopathies can form.

According to the classification of the causes contributing to the development of osteopenia (osteoporosis) in children [6], in addition to intrauterine and young children's factors, there are numerous factors in both older children and adolescents:

1) Malnutrition, deficiency of protein, dairy products;
2) Hypovitaminosis;
3) Low-calcium diets;
4) Diseases of the gastrointestinal tract, kidneys, liver, rheumatic and endocrine disorders, etc.;
5) Smoking, beer and alcohol abuse.

In addition, osteopenia can be iatrogenic – as a result of medicine taking: systemic use of steroid hormones, thyroid hormones, anticonvulsants (phenobarbital, etc.), heparin (long-term therapy – 3 months or more), chemotherapeutic drugs, antacids with prolonged use (especially aluminum containing), etc. These factors affect peak bone mass formation, which can result in pathological osteomalacia with osteoporosis, high risk of bone deformities and fractures in young and elderly age.

The development of osteopenia or even osteoporosis in children is associated with rapid growth, a high rate of skeletal modeling, and also phosphates and calcium insufficiency and imperfections in their transport, metabolism, and utilization [9, 10]. In addition, there are certain age-specific critical periods of childhood, characterized by a high risk of bone mineral density reducing and fracture development [11, 12]. According to the study of 1510 children, the greatest frequency of osteopenia and osteoporosis is observed in adolescence. Osteopenia frequency was defined as 56.2%; osteoporosis was found in 6% children [12].

In children, osteoporosis is more often secondary, as a result of different diseases. Because of bone mass loss, both in primary and secondary osteoporosis, bone fractures have a typical localization: vertebral body, distal radius, proximal humerus, femoral neck and trochanteric area. In vertebral body, both true compression fractures and "creep" deformations in case of "fish vertebrae" formation due to microfractures occur.

Most common symptoms of osteoporosis are pain, height decrease, spine deformation, convulsions in the limbs. However, acute pain is more common for fracture, while dull pain in the bones or lower back, severe fatigue during prolonged exposure in one posture may be symptoms of osteoporosis. We acknowledge that among professional athletes, the issues of pain differentiating by its nature and etiology can be the subject of independent discussion, and "pain suffering" in sport is rather a lifestyle. Therefore, pain cannot be an informative clinical marker of osteoporosis in professional athletes.

Convulsion complaints are rarely accurate. The interpretation of these symptoms in athletics, multisport race, game sports (hockey, football, etc.) is complex and challenging. There are many causes for convulsions: electrolyte disorders, alteration of neuromuscular regulation, etc.

Height decrease is caused by reduction of vertebral bodies and spine "deflection". This clinical sign, as well as pain, is very doubtful, especially in the early stages of osteoporosis in young athletes.

Such symptoms as nails fragility and periodontal diseases can indicate osteoporosis predisposition and cannot be an objective clinical marker of early osteoporosis manifestation.

Thus, classical osteoporosis symptoms cannot be uniquely used for diagnosis verifying in professional athletes.

2. Bone Density Test in Children and Adolescents

According to practical medicine principles, the diagnosis of "osteoporosis" in children requires a history of clinically confirmed fractures of long tubular bones of upper and lower extremities, compression fractures of vertebral bodies, low bone mass or bone density. Bone mineral density test should be considered as part of the bone health assessment in patients with increased fracture risk of. Currently, there are four types of technologies for bone mineral density measuring:

1) Single X-ray absorptiometry (SXA);
2) Dual energy X-ray absorptiometry (DXA), including peripheral DXA (pDXA);
3) Radiographic absorptiometry (RA);
4) Quantitative computed tomography (QCT), including peripheral QCT.

In clinical practice, the "gold standard" for osteoporosis

diagnostics is X-ray absorptiometry [15]. Peripheral DXA is the most preferred method for bone mass and bone mineral density measurement in children and adolescents. In complex and unclear cases for the most accurate diagnosis in children and adolescents, it is recommended to measure bone mineral density and bone mineral mass in the lumbar spine or in the whole body. Whole body scan can be useful in identifying patients with chronic diseases or conditions that are associated with malnutrition (anorexia nervosa, inflammatory bowel disease) or with muscular and skeletal disorders (idiopathic juvenile osteoporosis, osteogenesis imperfecta).

Bone mineral density test in the proximal femur is an unreliable method for evaluating of bone tissue mineralization in growing children due to the considerable variability in skeletal development. In children with a delay in linear growth and development, the results of bone mineral density test in the lumbar spine and whole body should be analyzed according to absolute or normal-to-age height or should be compared with pediatric databases, including specific for age, sex and height Z-scores.

According to clinical recommendations (2009), osteoporosis in children should not be diagnosed by densitometry findings without bone fracture history [16]. The T-score should not be used to assess bone mineral density in children and adolescents. Bone mass reduction in comparison with the age norm can be diagnosed based on Z-score less than -2.0 SD. With Z-score more than -2.0 SD, bone mineral density consider to be within the age norm.

Despite the fact that DXA are the most studied and widely used in clinical practice, nevertheless this method has certain limitations. For example, osteoporosis diagnostics is possible only when a significant bone mass have lost. Even with the detection of low bone mineral density, it is not possible to identify all patients with high risk of bone fracture. If treat only patients (not juniors) who have osteoporosis, diagnosed according to the WHO classification (T-score $\leq$ 2.5 SD), many of those who will subsequently have a fracture will not be identified, and, therefore, the opportunity to prevent fracture will be missed [17]. Besides:

1) DXA does not allow predicting the level of bone density loss;
2) For the prediction of fractures in children, currently there is no precisely defined scores;
3) Measurement of changes in bone density is possible only after 1.5-2 years after therapy initiation, i.e. there is no possibility to monitor the effectiveness of the medicines.

It is remarkable that using of "bone densitometry" allow assessing basic parameters of bone tissue strength; however, these methods do not provide any information about the bone metabolism. The level of formation and resorption of bone tissue can be assessed in several ways: by measuring the enzymatic activity of bone cells (osteoblasts and osteoclasts) or by measuring degradation products of bone matrix, which are released into circulation during bone tissue exchange.

Based on the information provided, along with the measurement of bone mineral density, it is very relevant to assess biochemical markers of osteoporosis [18, 19]. We conducted a study to analyze osteoporosis risk factors and biochemical markers of osteoporosis, which are usually assessed during the detailed medical examination. The study, conducted in the Federal Scientific Clinical Center for Sports Medicine and Rehabilitation of the Russian Federal Medical-Biological Agency, included professional athletes, also under 18 years old.

Figure 1 shows concentration of Beta-CrossLaps (C-terminal telopeptide - collagen type I degradation product and bone resorption marker) in junior athletes in different age groups. As it can be seen in the figure, the level of Beta-CrossLaps exceeds the norm in all age groups, especially among 14-15-year-old athletes. In addition, it is necessary to mark that at the age of 14-15, boys have higher level of Beta-CrossLaps, but after 15, higher levels are observed in girls. Perhaps the increase of this marker is associated with the specific activity of metabolic processes in athletes at this age. The highest levels of Beta-CrossLaps are discovered in game and combat sport athletes (Figure 2).

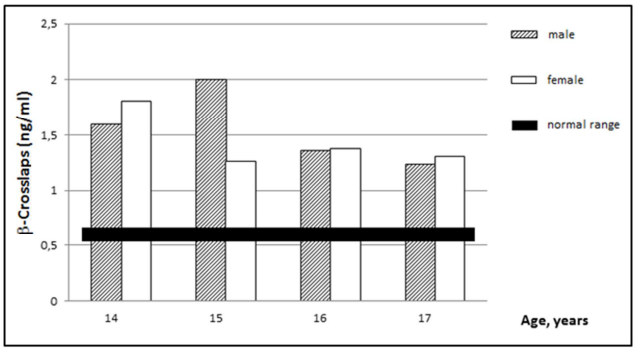

Figure 1. *Concentration of Beta-CrossLaps in junior professional athlete blood samples depending on sex and age.*

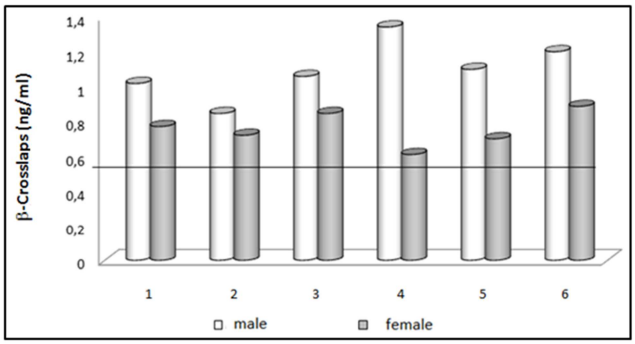

Figure 2. *Concentration of Beta-CrossLaps in junior professional athlete blood samples depending on type of sport.*

(0,6 ng/ml – upper limit of normal value)
1 - cyclic sports
2 - speed-strength sports
3 - high-coordination sports
4 - martial arts
5 – sport games
6 – multiathlon

Along with this, it is remarkable that the level of total calcium in the blood was within the normal reference values.

There were no differences in this indicator depending on the type of sport. The explanation for this phenomenon may be the fact that the blood calcium level is one of the most stable homeostasis constants of the human body. In pathophysiological reactions accompanied by increased intake and / or excretion of calcium, a powerful and multistage mechanism for maintaining its optimal level in the blood is induced [20]. That is why blood calcium level cannot be useful in osteoporosis diagnostics in athletes.

In our opinion, these factors, in addition to genetic, are the most significant risk factors for the osteoporosis development (especially for young athletes):

1) Low peak bone mass;
2) Female sex, late onset of menstruation, amenorrhea;
3) Low calcium intake;
4) Excessive physical activity;
5) Vitamin D deficiency.

A small number of studies are devoted to the problem of osteoporosis in professional athletes. Our analysis of worldwide data showed that in the PubMed/Medline database from 2011 to 2015 years, there were only 33 articles on this topic, and the peak of publication activity occurred in 2015. Thus, according to the worldwide data, the prevalence of osteoporosis (based on densitometry test) varies from 4.1% to 13%, with the largest rate discovered among professional dancers - 46.5% [21]. Along with this, it is remarkable that female athletes with decreased bone density, amenorrhea and anorexia have higher risk of osteoporotic fracture, which is called "Female Athlete Triad".

This term was proposed in 1993 by the American College of Sports Medicine. Today, the relationship between weight loss and amenorrhea is well studied. Amenorrhea in female athletes, according to some scientists, occurs because of hypothalamus dysfunction [22, 23]. The cessation of normal impulse secretion of gonadotropic, luteinizing and follicle-stimulating hormones can be a consequence of the negative energy balance of the body. The absence of impulse secretion of these hormones suppresses the production of estradiol by the ovaries, which leads to the termination or absence of menstruation.

It is known that female athletes with amenorrhea have a significantly lower bone density than women with normal menstrual cycles, i.e. the risk of fracture for them is much higher. The degree of bone density reduction in female athletes, who did not have menstruation for more than 6 months, is close to that in postmenopausal women. Such bone density decrease can be irreversible and have long-term consequences. When comparing the frequency of fatigue fractures that occurred in the same time interval for the same total run in female runners with amenorrhea and runners with a normal menstrual cycle, it has been shown that fractures appears more often in the absence of menstruation [24].

Despite the fact that the sports triad is described in female athletes, some symptoms of this condition also occur in men. In this regard, IOC experts propose to use a broader term to describe the state associated with the manifestation of a relative energy deficit in sport (RED-S). RED-S syndrome is caused by the violation of physiological functions and is accompanied by metabolic and immune abnormalities, osteoporosis, a violation of protein synthesis and changes in the cardiovascular system. This energy deficit is associated with a violation of the balance between the incoming energy and the energy expended during normal life and physical activity [25].

Along with a sufficient vitamin D intake, it is also necessary to take into account the adequate supply of the athlete's body with calcium. It is known that low calcium intake is a risk factor for the osteoporosis development. However, the real calcium intake in juniors is significantly below the norm, which requires appropriate nutritional support. For example, the Department of Pediatrics of Russian National Research Medical University showed that the calcium intake in the diet of modern adolescents is 3 times lower than the required daily intake: 418 mg vs. 1500 mg per day [26].

The significance of vitamin D deficiency is convincingly proved in connection with increased traumatization of bones and joints with the chronic osteoarthritis as outcome; the formation of immune disorders and, as a result, frequent infectious diseases; chronic stress; risk of impaired glucose tolerance and/or development of diabetes mellitus and some other clinically and socially significant conditions [27-29].

Thus, in our opinion, in the osteoporosis diagnostics in athletes of the Russian national teams, it is relevant to use biochemical markers of this disease, taking into account the relevant risk factors. Since the study of some biochemical parameters is part of the detailed medical examination program, and the analysis of the results should not be challenging for the physician, it can allow identifying high-risk groups, verify the diagnosis and prescribe appropriate treatment. In addition, unlike densitometry, which measures the level of bone tissue mineralization at the time of the study, biochemical markers allow us to assess the rate and direction of the bone metabolism processes.

3. Medications for Osteoporosis

Not only the osteoporosis diagnostics, but also the osteoporosis treatment in professional athletes, especially juniors, remains a big issue. In clinical practice, there are three groups of drugs, which are used to treat osteoporosis [30]:

1. Drugs that slow down the processes of bone destruction (calcium salts, bisphosphonates, calcitonin, estrogens, selective modulators of estrogen receptors).
2. Drugs that enhance the bone tissue synthesis (fluoride medications, anabolic steroids, androgens, growth hormone, parathyroid hormone).
3. Drugs that simultaneously slow down the processes of destruction and enhance the synthesis of bone tissue (Vitamin D, ossein-hydroxyapatite compounds, strontium ranelate).
4. However, in sports medicine it is important to take into account that not all medications of these groups are

allowed for use in professional athletes. The table contains a list of medications approved and prohibited for use in professional athletes [31].

Table 1. *Medications for osteoporosis treatment approved and prohibited For use in professional athletes.*

Medication group	Medications, prohibited for use by the WADA (2017)	Medications, approved for use by the WADA (2017)	Example of medicines (INN), approved for use by the WADA, age restrictions
1	Anabolic steroids, androgens, growth hormone	Calcium salts	Calcium glycerophosphate (from 2 years), Calcemin (from 5 years), Calcemin Advance (from 5 years).
		Bisphosphonates	Etidronic acid (from 3 years), Ibandronic acid (from 18 years).
2		Calcitonin	Calcitonin solution for injection (from 18 years).
		Estrogens	Lactobacteria + estriol + progesterone (from 18 years).
		Selective modulators of estrogen receptors	Indolcarbinolum (from 18 years).
		Fluoride medications	Sodium fluoride (from 2 years).
		Parathyroid hormone	Parathyroid hormone (from 18 years).
3		Vitamin D	Alphacalcidol (from 3 years), Calcitriol (from 3 years), Colecalciferol, aqueous and oily solution (without age restrictions).
		Ossein-hydroxyapatite compounds	Osteogenon (from 18 years).
		Strontium ranelate	Strontium ranelate (from 18 years).

The first group of drugs for the treatment of osteoporosis in juniors and approved by the WADA for use include calcium salts. This pharmacological group is rather widely represented in the pharmacological market [32]: calcium glycerophosphate, calcium gluconate, calcemin, calcemin advance, etc.

Fluoride preparations registered in the state register of medicines include sodium fluoride. Registration of the combined form of sodium fluoride + malic acid (Xerodent), approved for use from the age of 12, ended in 2016 (in Russia). The field of use is only dentistry.

The scientific papers describe the use of calcitonin in children, with the advantage given to intranasal forms. However, the described connection of calcitonin intake and increased risk of oncological diseases in adults limits its use in children [33].

4. Conclusion

Thus, it can be concluded that osteoporosis, as a pathophysiological process, is extremely relevant for professional athletes. A special risk group for the osteoporosis development is represented by juniors, not only because of inadequate intake of calcium and vitamin D, but also because of excessive physical activity in the background of the pubertal period - period of maximum body transformations. It is necessary to change not only diagnostic criteria, but also preventive and treatment strategies, which will take into account the specifics of sports, gender differences, and the age of athletes.

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