# SECONDARY HYPERPARATHYROIDISM ASSOCIATED WITH VITAMIN D DEFICIENCY IN YOUNG HIGHLY TRAINED ATHLETES

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Vitamin D deficiency that remains non-compensated for a long time is associated with high risk of rickets in children and osteomalacia in adults, myopathies and low-energy fractures, as well as secondary hyperparathyroidism (SHPT). SHPT represents one of the main mechanisms, through which vitamin D deficiency can contribute to pathogenesis of low-energy fractures. The study was aimed to assess the calcium and phosphorus metabolism state and the bone tissue metabolism markers in highly trained athletes with SHPT, as well as the prevalence of SHPT in elite sports. The study involved 527 young athletes aged 12–18 years (average age 15.2 years) doing 32 sports. The group with SHPT included 16 children (11 girls and 5 boys) with the average age of 15.0 years. The control group with normal levels of parathyroid hormone consisted of 511 children (254 boys and 273 girls) with the average age of 15.2 years. The studied subgroups were matched by age ($p$ = 0.678). Girls predominated in the group with SHPT ($p$ = 0.02). SHPT associated with vitamin D deficiency was revealed in 3% of young highly trained athletes, it was more prevalent among girls. The SHPT development does not result in alteration of the calcium and phosphorus metabolism indicators, however, it is accompanied by the increase in bone resorption markers, β-CrossLaps and total alkaline phosphatase. Many aspects related to vitamin D deficiency in SHPT are currently poorly understood, and there are no clinical guidelines on the cholecalciferol replacement therapy. Large-scale clinical trials are required to determine the optimal threshold values of 25(OH)D3 and the powerful and effective treatment regimens for young athletes having SHPT associated with vitamin D deficiency.

**Keywords:** children, young athletes, sports medicine, secondary hyperparathyroidism, vitamin D deficiency

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**Compliance with the ethical standards:** the study was approved by the Ethics Committee of the Gaaz Moscow Medical and Social Institute (protocol No. 4 dated 04 October 2021). The athletes' parents/caregivers or legal representatives submitted the informed consent to participation in the study.

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# ВТОРИЧНЫЙ ГИПЕРПАРАТИРЕОЗ НА ФОНЕ ДЕФИЦИТА ВИТАМИНА D У ЮНЫХ ВЫСОКОКВАЛИФИЦИРОВАННЫХ СПОРТСМЕНОВ

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Длительно некомпенсированный дефицит витамина D сопряжен с высокими рисками развития рахита у детей и остеомаляции у взрослых, миопатий и низкоэнергетических переломов, а также вторичного гиперпаратиреоза (ВГПТ). ВГПТ — один из основных механизмов, посредством которых дефицит витамина D может вносить вклад в патогенез низкоэнергетических переломов. Целью работы было изучить состояние фосфорно-кальциевого обмена и значения маркеров метаболизма костной ткани у высококвалифицированных спортсменов с ВГПТ, а также его распространенность в спорте высших достижений. В исследование включено 527 юных спортсменов в возрасте 12–18 лет (средний возраст 15,2 лет), занимающихся 32 видами спорта. В группу с ВГПТ вошло 16 детей (11 девочек и 5 мальчиков); средний возраст 15,0 лет. Контрольную группу с нормальным уровнем паратиреоидного гормона составили 511 детей (254 мальчика и 273 девочки); средний возраст 15,2. Исследуемые подгруппы не различались по возрасту ($p$ = 0,678). В группе ВГПТ преобладали девочки ($p$ = 0,02). ВГПТ на фоне гиповитаминоза D у юных высококвалифицированных спортсменов был выявлен в 3% случаев и чаще встречался у девочек. Развитие ВГПТ не приводит к изменению показателей фосфорно-кальциевого обмена, однако сопровождается повышением маркеров костной резорбции — β-CrossLaps и общей щелочной фосфатазы. Многие аспекты, связанные с дефицитом витамина D при ВГПТ, в настоящее время не изучены, а клинические рекомендации по заместительной терапии колекальциферолом у юных спортсменов отсутствуют. Необходимо проведение крупных клинических исследований для определения «оптимальных «пороговых» уровней 25(OH)D3 и действенных, эффективных схем лечения у юных спортсменов с ВГПТ на фоне гиповитаминоза D.

**Ключевые слова:** дети, юные спортсмены, спортивная медицина, вторичный гиперпаратиреоз, дефицит витамина D

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The population-based studies suggest high prevalence of low vitamin D status both in pediatric population and among young elite athletes [1–3]. Vitamin D supply is fundamentally important to maintain children's health. This is due to the fact that viramin D is used not only for treatment of rickets, but also to maintain lipid metabolism, prevent obesity, cardiovascular disorders, maintain anti-infection immunity; vitamin D deficiency is also associated with high risk of secondary hyperparathyroidism (SHPT). SHPT represents one of the main mechanisms, through which vitamin D deficiency can contribute to pathogenesis of low-energy fractures [4, 5].

Today, there are no statistical data on the state of calcium and phosphorus metabolism and the values of bone tissue metabolism markers in young elite athletes with SHPT in the Russian Federation; the prevalence of SHPT is still poorly understood.

The study was aimed to assess the state of calcium and phosphorus metabolism and bone tissue metabolism in SHPT and determine the prevalence of SHPT in young highly trained athletes.

## METHODS

A cross-sectional single center study involving young athletes, members of national teams of the Russian Federation, who underwent in-depth medical assessment at the Federal Research and Clinical Center for Children and Adolescents between March and June 2022, was conducted.

Inclusuion criteria: elite atletes – members of national teams of the Russian Federation aged 12–18 years.

Exclusion criteria: history of acute respiratory viral infection or other disease resulting in missing three or more training sessions within 30 days before assessment.

Serum levels of 25-hydroxycalciferol (25(OH) D3), parathyroid hormone (PTH), C-telopeptide (β-CrossLaps), total alkaline phosphatase (ALP), total calcium, phosphorus, and magnesium were measured in all young athletes. The 25(OH) D3 and PTH levels were measured by the Chemiluminescent Microparticle Immuno Assay (CMIA) using the specialized kits (Abbott Laboratories; USA). The concentration of 25(OH)D3 ≥ 30 ng/mL was considered to be normal, vitamin D insufficiency was diagnosed when the concentration was 20–29.9 ng/mL, deficiency was diagnosed at 10–19.9 ng/mL [6]. The PTH reference range for children aged 9–18 years was 2.32–9.28 pmol/L. Assessment of β-Cross laps and total ALP was performed by the electrochemiluminescence assay using the Cobas e 411 analyzer (Roche Diagnostics; Germany). The value < 0.584 ng/mL was considered to be the upper end of the β-CrossLaps reference range for the general population. The total calcium, phosphorus, and magnesium levels were measured using the Indiko Plus automatic analyzer (Thermo Fisher Scientific; USA). Sexual development was estimated using the Tanner classification.

The following parameters were considered to be the major endpoints of the study: SHPT rate, serum levels of PTH, β-CrossLaps, total ALP, 25(OH)D3, and total calcium in the young highly trained athletes.

All study participants were divided into two subgroups according to the presence of SHPT.

SHPT was diagnosed in cases of the parathyroid hormone (PTH) levels exceeding > 9.28 pmol/L in combination with the decreased 25(OH)D3 levels.

Statistical processing of the results was performed using the Statistica version 10.0 software package (StatSoft Inc.; USA).

Since the distribution of the studied quantitative indicators was non-normal (based on the Kolmogorov–Smirnov test), all data are presented as the median (Me) and 1st and 3rd quartiles [$Q_1$; $Q_3$]. The Mann–Whitney U test and Kruskal–Wallis test were used to assess significance of differences in quantitative traits. Qualitative traits are presented as the percentage (%) with an absolute value. Contingency tables were compiled to assess the differences between qualitative traits, which was followed by assessment based on the Pearson's chi-squared test ($\chi^2$). The differences were considered significant at $p \leq 0.05$.

## RESULTS

A total of 527 young athletes aged 12–18 years engaged in 32 sports were included in the study. The group with SHPT included 16 children (11 girls and 5 boys); average age 15.0 [14.1; 16.2] years. The comparison group with normal PTH levels consisted of 511 children (254 boys and 273 girls); average age 15.2 [14.2; 16.5] years. The studied subgroups were matched by age ($p = 0.678$), body height ($p = 0.124$), and body weight ($p = 0.632$), however, their sexual development stages were different. Girls with incomplete sexual development prevailed in the group with SHPT, while 86% of the comparison group had compete puberty. The clinical characteristics of the studied subgroups are provided in Table 1.

Elevated PTH levels were revealed in 16 young athletes, which accounted for 3% of surveyed individuals. SHPT was twice more often detected in girls, than in boys (11 vs. 5; $p = 0.034$). The average PTH levels of athletes with SHPT were 10.2 pmol/L, with individual fluctuations within the range of 9.3–11.4 pmol/L. The average PTH levels of athletes engaged in certain sports turned out to be comparable ($p = 0.14$; Fig. 1)

Elevated PTH levels were revealed in the athletes engaged in such sports, as rhythmic gymnastics (4 individuals), boxing (3 individuals), wrestling, synchronized swimming, figure skating, softball (2 individuals), and volleyball (1 individual).

Then we assessed the indicators that characterized the state of calcium and phosphorus metabolism and bone tissue metabolism.

**Table 1.** Clinical characteristics of the studied subgroups

| | SHPT group | Comparison group (normal PTH levels) | *p* |
|---|---|---|---|
| Number, *n* | 16 | 511 | – |
| Sex: m/f | 5/11 | 254/273 | 0.021 |
| Age | 15.0 [14.1;16.2] | 15.2 [14.2;16.5] | 0.678 |
| Body height, m | 1.66 [1.61; 1.7] | 1.72 [1.65; 1.79] | 0.124 |
| Body weight, kg | 57 [48.0; 69.0] | 52 [45; 65] | 0.632 |
| Sexual development:<br>Tanner stage 1<br>Tanner stage 2–3<br>Tanner stage 4–5 | –<br>7 (43%)<br>9 (57%) | 6 (1%)<br>67 (13)<br>438 (86%) | –<br>0.001<br>0.001 |

The serum levels of total calcium ($p$ = 0.351), phosphorus ($p$ = 0.692), and magnesium ($p$ = 0.751) of young athletes with SHPT and their peers with normal PTH levels turned out to be comparable (Table 1).

A significant decrease in the 25(OH)D3 levels relative to the control group was revealed in young athletes with SHPT ($p$ = 0.0002; Table. 1). The prevalence of vitamin D deficiency turned out to be significantly higher in the group of young athletes with SHPT, than in their peers with normal PTH levels ($p$ = 0.021; Fig. 2). No normal vitamin D levels were revealed in young athletes with SHPT. Vitamin D insufficiency was reported in the group with SHPT and the control group in 19 and 42.2% of cases, respectively ($p$ = 0.072).

When assessing markers of bone metabolism, we found that athletes with SHPT had the increased levels of bone resorption markers relative to the comparison group (Table 2). The median β-CrossLaps value of young athletes with SHPT was 1.71 ng/mL, and the maximum values reached 2.6 ng/mL. The increase in ALP activity was also revealed in the group with SHPT (208.1 vs. 155.1 U/L; $p$ = 0.037).

## DISCUSSION

In our study, the prevalence of SHPT among young athletes was 3%. Furthermore, 81% of young athletes having elevated PTH levels were diagnosed with vitamin D deficiency. We have found no similar studies focused on assessing the rate of SHPT in elite sports in the available literature. However, considering high prevalence of hypovitaminosis D among athletes engaged in various sports demonstrated in many studies [2–4], it can be assumed that the problem of SHPT in professional sports is systemic.

It is well known that SHPT results from abnormal stimulation of excess PTH production by the parathyroid glands. Uremic and non-uremic etiological variants of SHPT are distinguished. Uremic SHPT represents PTH hypersecretion developing against the background of chronic kidney disease [7]. This SHPT variant is not typical for highly trained athletes. The subgroup of non-uremic causes includes primarily vitamin D deficiency or vitamin D metabolism disorder (decreased activity of the calcium-sensing (CaSR) and vitamin D-sensing (VDR) receptors in the parathyroid glands; bone tissue resistance to the PTH calcemic effect or fibroblast growth factor 23 (FGF-23)) [7].

Hypovitaminosis D results in the reduced intestinal calcium absorption and, therefore, paves the way for hypocalcemia. In response to this, the PTH-associated mechanisms aimed to stimulate osteoclastic bone resorption with the release of calcium and phosphate that increase calcium reabsorption in the kidney distal tubules are activated [8]. The increase in bone tissue resorption associated with SHPT is inter alia mediated by the effect of 1.25(OH)2D3, an active vitamin D metabolite capable of inducing expression of the RANKL TNFα-like factor (activator receptor of the NF-kB ligand) activating osteoclasts, from chondrocytes, osteoblasts and osteocytes. Furthemore, 1.25(OH)2D3 modulates expression of the factors regulating mineralization, such as Spp1 (osteopontin), MGP (matrix Gla protein), ENPP1 (ectonucleotide pyrophosphatase/phosphodiesterase 1), and ENPP2, as well as ANK (progressive ankylosis protein) and ALPL (intestinal alkaline phosphatase) [9].

Thus, vitamin D deficiency leads to the increased PTH secretion to maintain calcium homeostasis, which is due to the increased intensity of resorptive processes in the bone tissue. The above mechanisms lead to the decrease in the bone mineral density (BMD), including in children and adolescents. According to the data provided by the group of Korean authors, who have analyzed bone tissue condition in 1063 adolescents, the increase in the 25(OH)D3 levels is associated with the

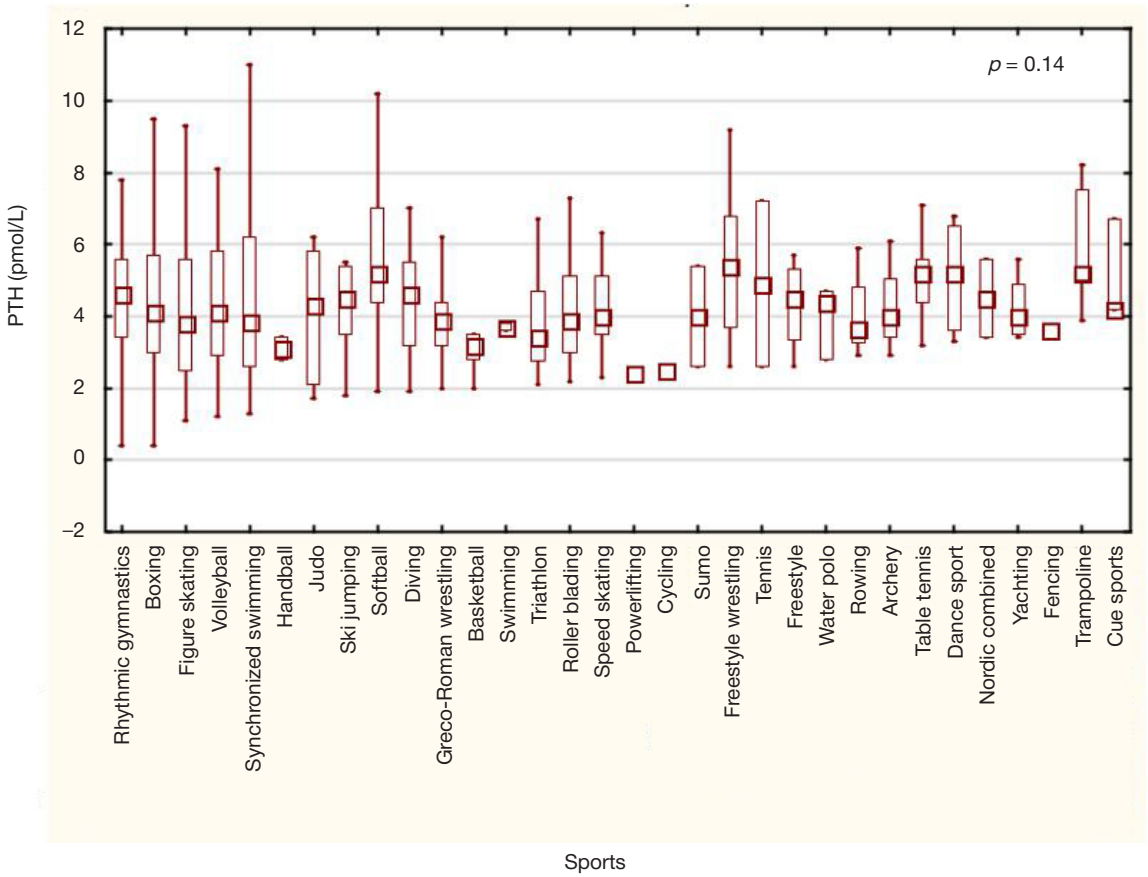


**Fig. 1.** Parathyroid hormone levels in young athletes engaged in certain sports

**Table 2.** Parameters of calcium and phosphorus metabolism and markers of bone tissue metabolism in young elite athletes depending on secondary hyperparathyroidism

| | SHPT group *n* = 16 | Comparison group (normal PTH levels) *n* = 511 | *p* |
|---|---|---|---|
| Total calcium, mmol/L | 2.48 [2.43; 2.58] | 2.52 [2.46; 2.58] | 0.351 |
| Phosphorus, mmol/L | 1.47 [1.45; 1.54] | 1.42 [1.28; 1.58] | 0.692 |
| Magnesium, mmol/L | 0.80 [0.77; 0.84] | 0.80 [0.77; 0.85] | 0.751 |
| Total alkaline phosphatase, U/L | 208.1 [147.0; 270.0] | 155.1 [103.4; 227.9] | 0.037 |
| β-CrossLaps, ng/mL | 1.71 [1.17; 2.36] | 1.34 [0.92; 1.99] | 0.042 |
| PTH, pmol/L | 10.2 [9.3; 11.1] | 4.1 [3.2; 5.4] | <0.0001 |
| 25(OH)D3, ng/mL | 15.6 [12.3; 19.3] | 21.5 [17.0; 26.7] | 0.0002 |

significant increase in the BMD Z-score in the lumbar spine and femoral head [10].

The meta-analysis including more than 7500 children from 23 studies has shown that the drop of 25(OH)D3 levels below 20 ng/mL is associated with the increased risk of fractures [11].

SHPT is one of the main mechanisms, through which vitamin D deficiency may contribute to the pathogenesis of low-energy fractures [4, 5].

However, the 25(OH)D3 threshold (cutoff point), at which PTH clearly begins to increase, remains undefined [12]. High variability of the 25(OH)D3 levels, at which PTH levels decrease, is reported [13]. According to some data, serum PTH concentrations start to decrease, when the 25(OH)D3 levels increase to 15–20 ng/mL, and are maximally depressed at the values of 30–40 ng/mL [14, 15]. According to other data, the threshold serum 25(OH)D3 level of 30 ng/mL is essential for prevention of SHPT and bone mineral density reduction [16]. These data contradict the results showing that PTH levels reach a plateau, when the 25(OH)D3 level is 17 ng/mL [17]. The 25(OH)D3 threshold of 12 ng/mL essential for preservation of bone tissue health in adults was established based on the ROC analysis data [18]. However, all the above studies were conducted in the adult population with the usual amount of physical activity, and these cannot be confidently extrapolated to the cohort of highly trained athletes.

The data on the PTH reference ranges for athletes are controversial. A number of authors report that the athletes' PTH levels are elevated compared to that of their peers with usual amount of physical activity. However, other studies have shown that PTH concentration remains unchanged or increases during physical activity [19–21].

Normal to low normal calcium levels and decreased phosphorus levels are typical for SHPT associated with vitamin D deficiency [4]. In our study, the development of SHPT in young athletes was not associated with the calcium and phosphorus metabolism disorder.

The study conducted revealed elevated β-CrossLaps and total ALP levels reflecting the activity of bone resorption processes in young athletes with SHPT. However, 43% of young athletes in the group with SHPT had incomplete sexual development characterized by active bone tissue metabolism. Thus, the identified differences in the course of puberty can explain the increase in bone metabolism markers in the group of young athletes with SHPT. When assessing bone metabolism markers in children and adolescents, it is necessary to consider that a pronounced imbalance between osteoresorptive and osteosynthetic processes due to active bone tissue growth is reported in children. The above age-related features explain higher values of bone metabolism markers in children compared to adults.

Assessment of β-CrossLaps levels in young highly trained athletes demonstrated the increase in this indicator in all age groups, especially in the 14–15-year-old athletes (Fig. 1). The average β-CrossLaps levels of athletes 2–3 times exceed the reference values for individuals with usual levels of physical activity [22]. The authors explain the increase in this marker by

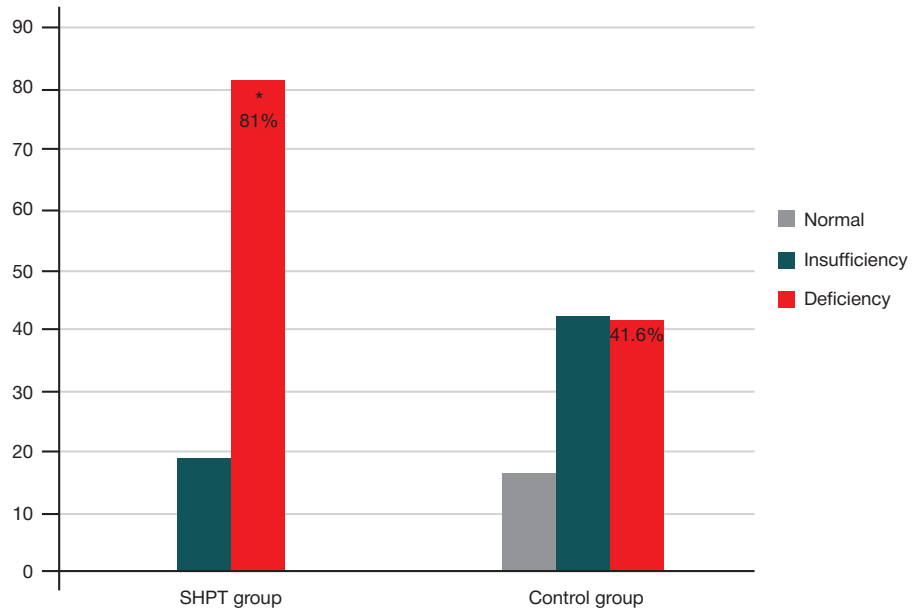


**Fig. 2.** Vitamin D supply in the studied groups. * — *p* = 0.021

the anabolic orientation of metabolic processes in the young athlete's body. When performing assessment based on the nature of sports activity during our study, it was also shown that the highest β-CrossLaps levels were found in representatives of combat sports and team sports; the average β-CrossLaps levels were higher in males, that in females [22].

ALP levels are widely used in clinical practice to diagnose disorders of bone remodeling. It is advisable to determine acidic ALP when assessing bone metabolism, since it is the only isoenzyme that is invoved in bone matrix mineralization and demonstrates metabolic activity of osteoblasts. According to the literature the concentration of bone ALP correlates with blood levels of ionized calcium, while the dynamic changes in blood ALP levels characterize the changes in bone mineral density [23, 24]. The total ALP increase in nonspecific, it can be found in various conditions, including some tumors and hepatobiliary diseases.

Thus, clinical assessment and interpretation of bone metabolism markers in young highly trained athletes is difficult. Currently, this does not allow to use these as reliable biomarkers of the disorders of bone tissue remodeling.

The season, when blood was collected for 25(OH)D3 testing, is an important limitation of this study. Hypovitaminosis D is most prevalent in spring, which could affect low vitamin D supply in the studied cohort. Furthermore, there are no data on taking cholecalciferol and other dietary supplements by young athletes at the time of blood collection.

The changes in bone tissue metabolism markers (β-CrossLaps and total alkaline phosphatase) revealed in the studied subgroups can result from the children's growth and the features of physical exertion in certain sports, which does not allow us to objectively estimate the contribution of SHPT to variability of these indicators.

## CONCLUSIONS

SHPT associated with hypovitaminosis D is found in 3% of young elite athletes and more prevalent among girls, than boys. The development of SHPT does not lead to changes in the indicators of calcium and phosphorus metabolism, however, it is associated with the increase in bone resorption markers (β-CrossLaps and total ALP). Many aspects related to vitamin D deficiency in SHPT are currently poorly understood; there are no clinical guidelines on cholecalciferol replacement therapy in young athletes. It necessary to conduct large-scale clinical trials to determine optimal threshold levels of 25(OH)D3 and effective treatment regimens for young athletes with SHPT associated with hypovitaminosis D.

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