Vitamin D Levels During Fracture Healing in Children

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Summary

To evaluate vitamin D levels in children treated with fractures during the healing period. A four-year prospective study, including healthy children treated with diaphyseal fracture of femur or forearm bones. Vitamin D levels were examined four times: at the time of the injury and then one, three, and five months after the injury, together with P1NP, ALP, GGT, and parathormone. In the beginning, patients were blindly divided into two groups, one supplemented with vitamin D3 for the entire follow-up period, the other non-supplemented. Altogether, 107 children underwent examination at the time of their injuries. Of these, 63 were included in the study and examined for the entire follow-up period – 36 supplemented, 27 non-supplemented. At the time of injury, 42 % had a deficit of vitamin D, 36.5 % had insufficiency, only 21.5 % had normal levels. In the children supplemented with cholecalciferol, vitamin D levels increased statistically significantly during the follow-up period (already after 1 month), in contrast with non-supplemented patients, where they did not. When we divided patients according to the initial vitamin D levels (deficit/insufficiency/normal levels) or fracture type (femur/forearm), we also observed significantly better results in supplemented groups. We observed a high prevalence of vitamin D deficit or insufficiency in healthy children at the time of their injuries. Patients supplemented with vitamin D3 had normal levels already after one month and this persisted throughout the follow-up period, in contrast with non-supplemented patients. Therefore, we recommend vitamin D testing and administration for children treated for fractures.

Keywords

Vitamin D • Pediatric fracture • Children • Vitamin D supplementation

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Introduction

When a bone is broken, a biological process called fracture healing begins immediately and this complex process can be divided into four partially overlapping stages: first we observe an inflammation stage, followed by the formation of soft callus (fibrous, then cartilaginous). The third stage is the genesis of a hard (bone) callus (visible on X-rays), and the last stage is the remodeling of the bone. We distinguish between primary and secondary healing. In the case of primary healing, the callus does not form at all, and we observe the primary healing in the case of anatomical reduction and fragment compression. Secondary healing includes all four aforementioned stages and is more common in the treatment of pediatric fractures (conservative treatment of fractures or minimally invasive osteosynthesis) [1].

The role of vitamin D is significant in regulating calcium metabolism, maintaining bone homeostasis, or bone mineralization. This is necessary for the formation of hard callus and bone remodeling. The influence of vitamin D can therefore be assumed at least in the last two stages of bone healing [2 - 3].

Vitamin D3 is produced mainly in the skin from 7-dehydrocholesterol during the absorption of photons of UV radiation type B (wavelength 290 – 315 nm). Previtamin D3 is formed, which spontaneously isomerizes

to cholecalciferol and (bound to the appropriate globulin) is transported to the liver. There, the hydroxylation of cholecalciferol at position 25 produces 25-hydroxycholecalciferol (calcidiol) and then in various tissues (mainly in the kidneys) the hydroxylation at position 1 produces the active form of vitamin D (1.25-dihydroxycholecalciferol, calcitriol). Its influence is then observed throughout the organism, among the most important functions in relation to bone mass and mineral metabolism are the effects on the kidneys (increases the reabsorption of calcium by the tubules), the parathyroid glands (by feedback activation of the "calcium-sensing receptor" suppresses the production of parathormone), the intestine (increases the absorption of calcium from the lumen), and bones (increases the resorption of older bone tissue and the deposition of calcium in newly formed bones) [4].

However, the effect of vitamin D on fracture healing is not sufficiently studied and described even nowadays, unlike the mentioned regulations under physiological conditions. At the same time, vitamin D deficiency is increasingly the subject of studies, especially its connection with autoimmune and other diseases, with rickets in children, osteomalacia in adults, or osteoporosis in the elderly population [5].

A plasma/serum level of 25-hydroxyvitamin D ≥ 75 nmol/l is stated as normal. As insufficiency of vitamin D is considered a plasma/serum level 50-75 nmol/l, lower levels (< 50 nmol/l) are reported as vitamin D deficiency [6].

Material and Methods

The prospective study lasted 4 years in total - from January 2017 to December 2019, and then from May 2021 to May 2022. It included Caucasian children (up to 18 years of age) with diaphyseal forearm fractures (radius, ulna, or both), treated with intramedullary osteosynthesis with Prévot nails according to the ESIN (elastic stable intramedullary nailing) technique, and patients with diaphyseal femur fractures, treated both nonoperatively by traction (Bryant`s vertical skin traction or proximal tibial skeletal oblique traction), as well as osteosynthesis according to the ESIN technique. All fractures were caused by a normal injury mechanism and appropriate force.

Inclusion criteria were informed consent to participate in the study and the fracture and method of treatment described above. Exclusion criteria were refusal to participate in the study, as well as disease or drug therapy known to affect bone quality and/or vitamin D levels and metabolism.

The reason for which the patient could have been excluded from the study during its course and no further follow-up took place was refracture during the follow-up, or his/her own (or legal representative`s) decision to end their participation.

All included patients had their serum levels of 25-hydroxyvitamin D, procollagen type 1 N-terminal propeptide (P1NP, which is a marker of bone formation), total alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT) repeatedly measured. These values were examined a total of four times - at the time of the injury, one month after the injury, three months after the injury, and five months after the injury. The parathormone level was measured once - one month after the injury.

Also, all patients underwent X-ray follow-ups to evaluate fracture healing, and this was compared with laboratory results, but this part is the subject of another study.

The monitored children were randomly divided into two groups (approximately the same size) even before the results of the first laboratory examination were known (blindly). One group was orally administered vitamin D3 – cholecalciferol throughout the follow-up (5 months). For supplementation, we used cholecalciferol in concentration of 0.5 mg/ml (“Vigantol”, manufactured by Merck KGaA), in a dose of 2 drops (=1000 IU = 25 ug) per day. The second group was not supplemented with vitamin D. Furthermore, it was possible to divide the patients into subgroups according to the type of fracture (and again supplemented/non-supplemented for each fracture) or initial vitamin D levels (deficit/insufficiency/normal levels).

Statistical analysis

The data are presented with descriptive statistics (average, median, minimum, maximum). Associations between variables were tested using the Mann-Whitney U test and the Friedman test. Subgroup analysis was tested using the Analysis of variance (ANOVA) model Repeated measures. Statistical analysis was performed using SPSS 29.0 software (SPSS Inc.). It was tested at a significance level of 0.05.

Results

A total of 107 children underwent at least one

examination of vitamin D, P1NP, ALP, and GGT levels. Of these, 44 patients were excluded during the study - 37 of them did not wish to take further blood tests and participate in the study, 5 were later treated in another hospital, and 2 children were excluded by the study investigator due to refracture during follow-up. For the remaining 63 patients included in the study, all samples were taken according to the study plan. In some of the excluded children, several blood samples were taken before they voluntarily withdrew from the study or were excluded due to refracture.

Altogether, 278 examinations were performed on 107 patients. The serum concentration of 25-hydroxyvitamin D from all these examinations was on average 66.9 nmol/l (23-181, median 62).

Deficit of vitamin D (<50 nmol/l) was present in 77 examinations (28 %). Vitamin D insufficiency (50-75 nmol/l) was found in 112 examinations (40 %) and normal levels of vitamin D (≥75 nmol/l) in 89 examinations (32 %).

At the first examination at the time of injury, 45 of 107 patients (42 %) had a deficit of vitamin D, 39 (36.5 %) had vitamin D insufficiency, and only 23 (21.5 %) had normal vitamin D levels.

Of the 63 children included in the study, 36 (57 %) were supplemented with vitamin D3 during the study period, 27 children (43 %) were without supplementation.

24 patients (38 %) with a femur fracture were included, of which 15 (62.5 %) were supplemented, 9 (37.5 %) were without supplementation.

With a forearm fracture, 39 patients (62 %) participated, of which 21 (54 %) were administered cholecalciferol, 18 (46 %) were not.

There were 20 girls and 43 boys included, and the average age was 8.3 years (1-16, median 8.5). In the femur fracture group (n=24), there were 7 girls and 17 boys, and the mean age was 4.8 years (1-14, median 3.3), in the forearm fracture group, there were 13 girls and 26 boys, and the mean age was 10.5 years (5-16, median 11).

All patients

In the 63 patients included in the study, the average level of vitamin D at the time of the injury was 57.3 nmol/l (27-134, median 50). After one month, 71.9 nmol/l (29-146, median 69.5). After three months, the average was 73.9 nmol/l (24-168, median 71). After five months, 68.2 nmol/l (23-181, median 65).

In the group of patients supplemented with vitamin D (n=36), the average level of vitamin D at the time of the injury was 54.4 nmol/l (27-106, median 49). After one month, 77.4 nmol/l (42-146, median 73.5). After three months, the average was 83.1 nmol/l (39-168, median 79). After five months, 81.3 nmol/l (40-181, median 77.5).

In the group of patients without vitamin D supplementation (n=27), the average initial vitamin D level was 61.1 nmol/l (31-134, median 54). After one month, 63.7 nmol/l (29-99, median 62). After three months, the average was 61.3 nmol/l (24-127, median 61). After five months, 51.2 nmol/l (23-76, median 49) (Fig. 1).

The initial plasma 25-OH vitamin D concentrations did not differ significantly between the study groups (p=0.550). In the group of patients supplemented with vitamin D, the vitamin D level changed statistically significantly during the follow-up period (p<0,001). After one month of administration, there was already a statistically significant increase (p<0,001); further changes were no longer statistically significant. In the group without supplementation, the level of vitamin D did not change statistically significantly during the follow-up period (p=0.328).

Patients with femur fractures

In the group of all patients in the study with femoral fractures (n=24), the average vitamin D level at the time of the injury was 60.8 nmol/l (33-116, median 51.5) After one month, 81.1 nmol/l (45-146, median 80). After three months, the average was 80.9 nmol/l (35-168, median 74.5). After five months, 79.3 nmol/l (40-181, median 69).

In the group of patients with femoral fractures supplemented with vitamin D3 (n=15), the average level of vitamin D at the time of the injury was 53.1 nmol/l (34-91, median 49). After one month, 84.3 nmol/l (53-146, median 80). After three months, the average was 87.1 nmol/l (52-168, median 85). After five months, 97 nmol/l (54-181, median 91).

In the group of patients with a femur fracture, without cholecalciferol supplementation (n=9), the average initial level of vitamin D was 73.6 nmol/l (33-116, median 59). After one month, 73 nmol/l (45-99, median 78). After three months, the average was 70.6 nmol/l (35-127, median 65). After five months, 56.6 nmol/l (40-68, median 53) (Fig. 2).

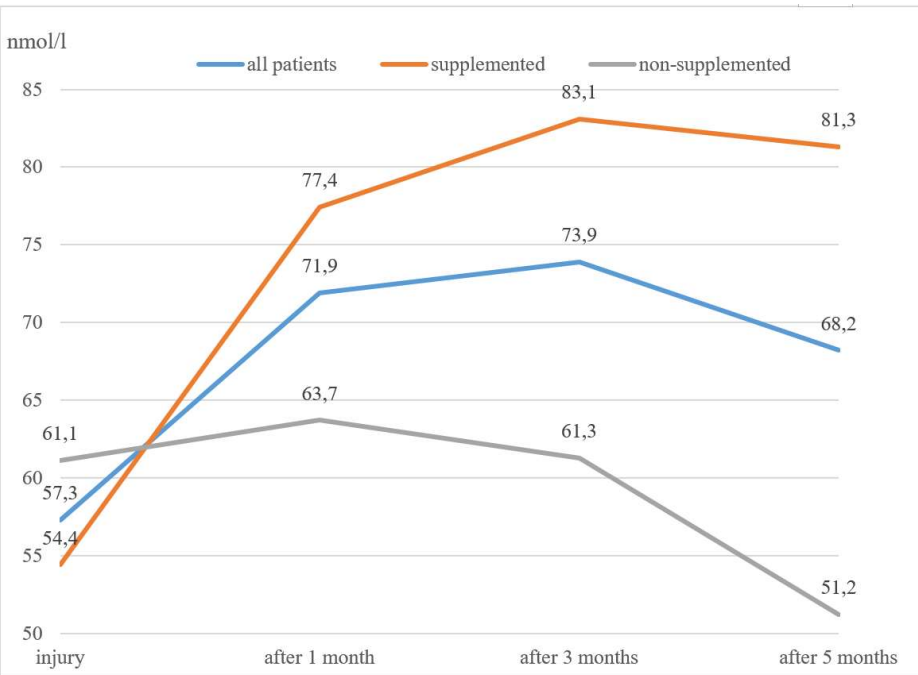

Fig. 1. Vitamin D levels, all patients

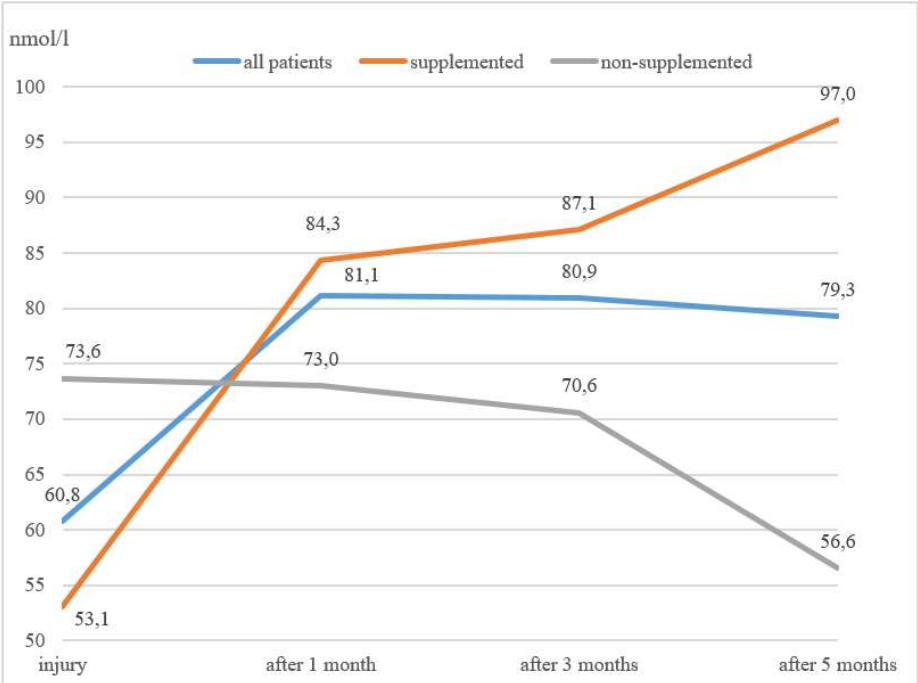

Fig. 2. Vitamin D levels, femur fractures

Patients with forearm fractures

In the group of all patients in study with forearm fractures (n=39), the average vitamin D level at the time of the injury was 55.1 nmol/l (27-134, median 49). After one month, 67 nmol/l (29-112, median 64). After three months, the average was 69 nmol/l (24-126, median 66). After five months, 60.5 nmol/l (23-112, median 55).

In the group of patients with forearm fractures supplemented with cholecalciferol (n=21), the average vitamin D level at the time of the injury was 55.3 nmol/l (27-106, median 47). After one month, 72.5 nmol/l (42-112, median 68). After three months, the average was 80 nmol/l (39-126, median 73.5). After five months, 70.5 nmol/l (40-112, median 69).

In the group of patients with forearm fractures, without vitamin D3 supplementation (n=18), the average initial level of vitamin D was 54.9 nmol/l (31-134, median 51). After one month, 60.6 nmol/l (29-98, median 61).

After three months, the average was 56 nmol/l (24-91, median 54.5). After five months, 47.5 nmol/l (23-76, median 47.5) (Fig. 3).

Patients who initially had a vitamin D deficiency

If we select only those patients who initially had a vitamin deficiency, we can observe the effect of their supplementation with cholecalciferol in this group.

Out of a total of 63 patients, 31 (49 %) had these values at admission. Of these, 19 were supplemented with vitamin D (61 %), the remaining 12 did not receive cholecalciferol (39 %).

The vitamin D level in the group of all these patients with a deficiency (n=31) was on average 40.8 nmol/l (27-49, median 41) at the time of the injury. After one month, 58.3 nmol/l (29-94, median 58). After three months, the average was 61.5 nmol/l (24-126, median 58.5). After five months, 56.5 nmol/l (23-112, median 53.5).

In the group of patients initially deficient who were then supplemented with vitamin D (n=19), the average initial vitamin D level was 41.5 nmol/l (27-49, median 43). After one month, 64 nmol/l (42-94, median 62). After three months, the average was 72 nmol/l (39-126, median 67). After five months, 65.6 nmol/l (40-112, median 63.5).

In the group of patients with vitamin D deficiency who continued without supplementation (n=12), the average level of vitamin D at entry was 39.6 nmol/l (31-49, median 38.5). After one month, 49.3 nmol/l (29-69, median 45.5). After three months, the average was 42.5 nmol/l (24-75, median 38). After five months, 45.1 nmol/l (23-67, median 46) (Fig. 4).

Patients who initially had vitamin D insufficiency

Similarly, we can observe the effect of cholecalciferol supplementation in a group of children who initially had vitamin D insufficiency.

Out of a total of 63 patients, 22 (35 %) had these values at admission. Of these, 13 were supplemented with vitamin D (59 %), the remaining 9 did not receive cholecalciferol (41 %).

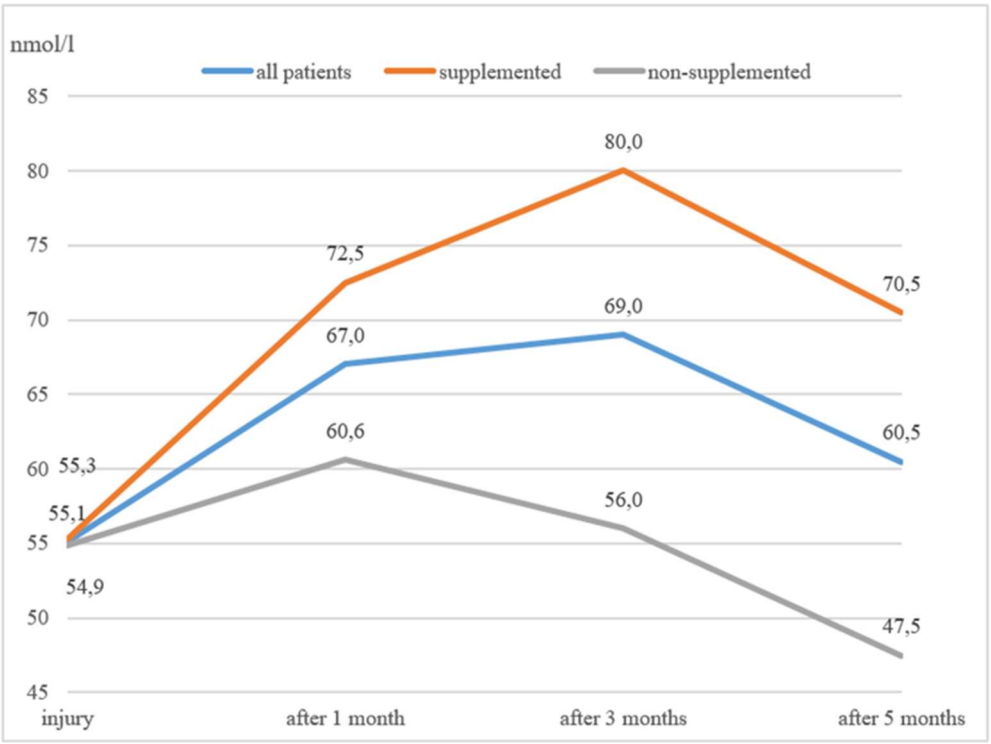

Fig. 3. Vitamin D levels, forearm fractures

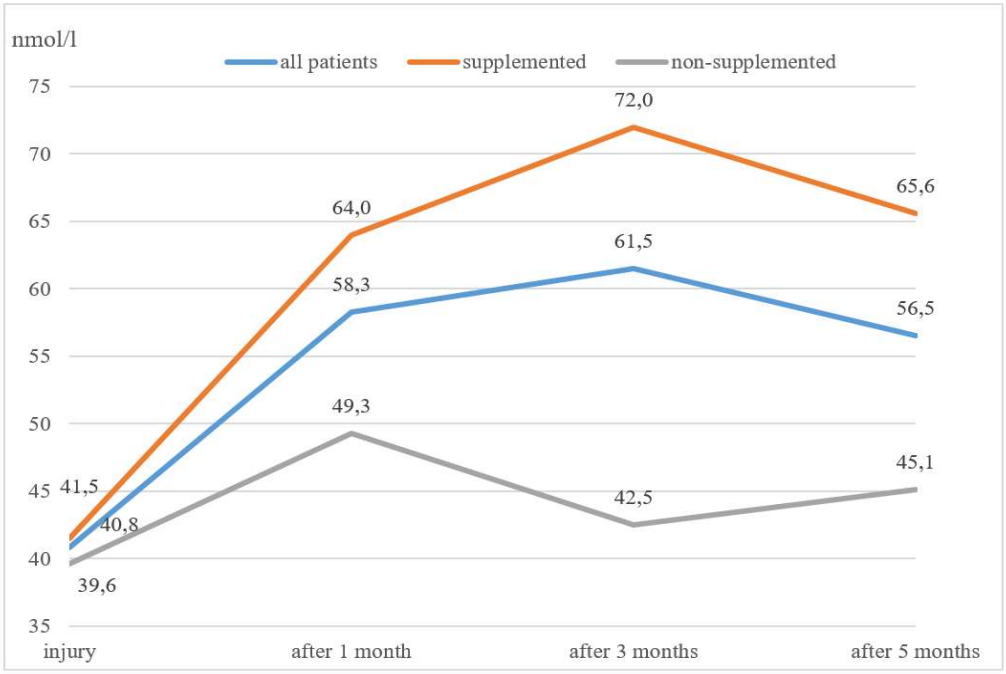

Fig. 4. Vitamin D levels, initially vitamin D deficiency

The level of vitamin D in the group of all these patients with insufficiency (n=22) was on average 60.6 nmol/l (50-73, median 58.5) at the time of the injury. After one month, 79.9 nmol/l (52-103, median 81). After three months, the average was 80.4 nmol/l (43-117, median 80). After five months, 79.3 nmol/l (40-181, median 76).

In the group of patients initially insufficient who were then supplemented with vitamin D (n=13), the average initial vitamin D level was 61.2 nmol/l (50-73, median 58). After one month, 84.3 nmol/l (55-103, median 86). After three months, the average was 87.8 nmol/l (60-112, median 92.5). After five months, 93.9 nmol/l (57-181, median 86).

In the group of patients with vitamin D insufficiency who continued without supplementation (n=9), the average vitamin D level at entry was 59.8 nmol/l (53-72, median 59). After one month, 73.6 nmol/l (52-99, median 72). After three months, the average was 70.6 nmol/l (43-117, median 62). After five months, 57.3 nmol/l (40-76, median 55.5) (Fig. 5).

Patients who initially had normal vitamin D levels:

The effect of cholecalciferol supplementation can also be observed in a group of children who had normal levels of vitamin D at the time of the injury.

Out of a total of 63 patients, 10 (16 %) had these values at admission. Of them, 4 were supplemented with vitamin D (40 %), the remaining 6 did not receive cholecalciferol (60 %).

In the group of all these patients with normal levels (n=10), the average vitamin D level at the time of the injury was 101.1 nmol/l (75-134, median 103.5). After one month, 107.1 nmol/l (84-146, median 104). After three months, the average was 94.8 nmol/l (64-168, median 84.5). After five months, 75.7 nmol/l (49-117, median 68).

In the group of patients with initially normal levels who were then supplemented with vitamin D (n=4), the mean vitamin D level at the time of the injury was 93.5 nmol/l (75-106, median 96.5). After one month, 119 nmol/l (104-146, median 113). After three months, the average was 119 nmol/l (96-168, median 106). After five months, 96 nmol/l (71-117, median 100).

In the group of patients with normal levels who remained without supplementation (n=6), the average vitamin D level was 106.2 nmol/l (81-134, median 107). After one month, 91.3 nmol/l (84-98, median 92). After three months, the average was 78.7 nmol/l (64-127, median 71.5). After five months, 55.3 nmol/l (49-65, median 52) (Fig. 6).

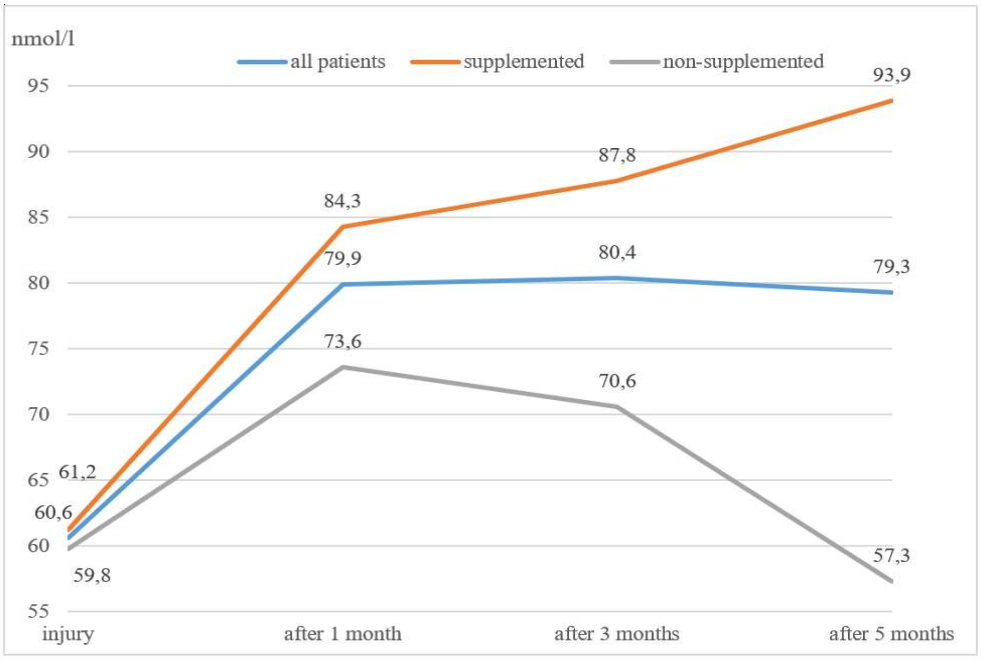

Fig. 5. Vitamin D levels, initially vitamin D insufficiency

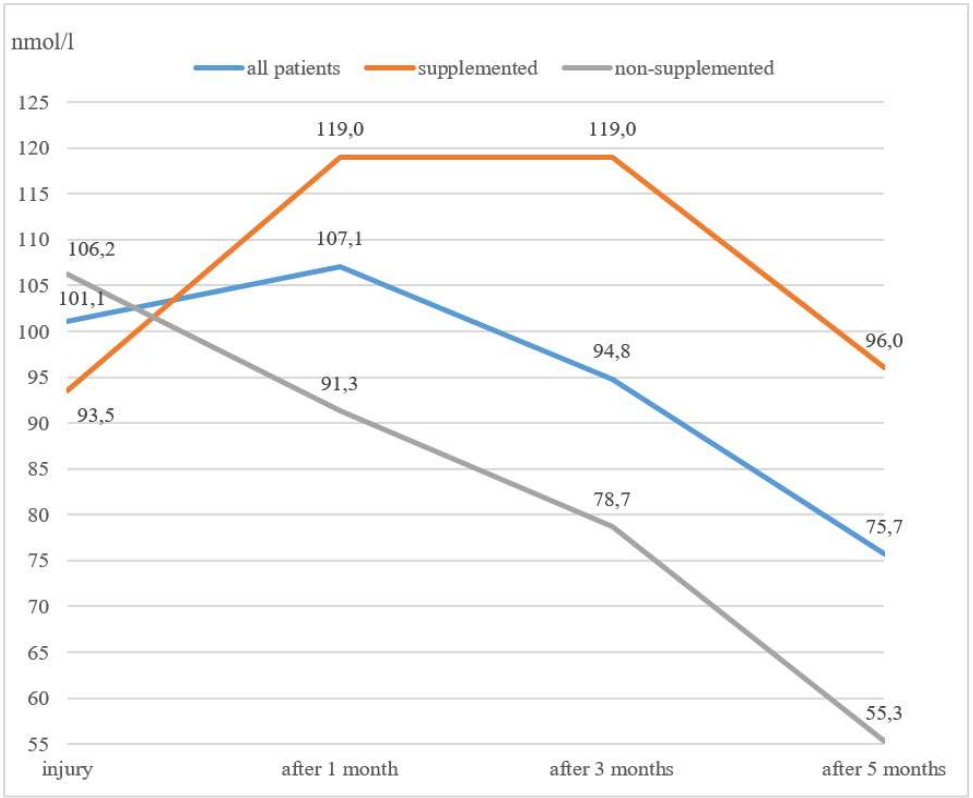

Fig. 6. Vitamin D levels, initially normal vitamin D levels

Discussion

After just one month of vitamin D3 administration, we observed a statistically significant difference in vitamin D levels between patients supplemented and not supplemented with cholecalciferol ($p<0,001$ in the supplemented group, $p=0.328$ without supplementation).

Our group of patients supplemented with vitamin D3 had, on average, values getting close to the border of vitamin D deficiency. After only one month of administration of cholecalciferol, their levels were within the range of normal values, where they remained also after three and five months.

In patients randomly assigned to the group without cholecalciferol supplementation, the initial levels were on average also in the category of vitamin D insufficiency, but significantly higher than in the supplemented group. In the following months, however, stagnation was observed in the non-supplemented group, or even a decrease close to the border of vitamin D deficiency after 5 months (Fig. 1).

When we divide children according to fracture type, in patients with femur fractures, there was a greater difference between the initial values, and therefore the difference in the following months was more significant in its difference, as well. In patients supplemented with vitamin D3, there was a permanent increase in average values, while without supplementation we observed a permanent decrease, at first moderate, then significant (Fig. 2).

In children with forearm fractures, on the other hand, the initial values were almost identical. In the following months, when supplementing with cholecalciferol, there is a clear increase in the first three months, although between the 3rd and 5th months, a further decrease is noticeable. Without supplementation, after a slight increase after one month, there is a permanent decrease to the level of vitamin D deficiency after 5 months (Fig. 3).

When we divide patients into three groups, according to their initial levels of vitamin D (deficit, insufficiency, or normal levels), we can observe the effect of their supplementation, as well. However, the number of patients in those subgroups is already lower and the possibility of statistical evaluation of the results is affected by this.

In the group of patients, who initially had a vitamin D deficiency, we can observe a difference between the supplemented/non-supplemented patients, where those with cholecalciferol supplementation reach the level of insufficiency and after 5 months even get close to normal levels (although they do not reach them, the maximum is 72 nmol/l), while those without cholecalciferol supplementation remain at the levels of vitamin D deficiency the whole time (Fig. 4). These groups are the biggest ones - a total of 31 patients, of which 19 had and 12 did not have supplementation.

In the group of patients who initially had a vitamin D insufficiency, we can observe a similar increasing trend both in supplemented and non-supplemented patients during the first month (although considerably higher in supplemented group, where there reach normal vitamin D levels, while in non-supplemented group, they only get close to the border of normal levels). After that, we observe a clear difference, where in those supplemented with cholecalciferol, the levels continue to increase up to the maximum of 93.9 nmol/l after 5 months, while in those without cholecalciferol, the levels start to decrease, still in the deficit levels, with the minimum of 57.3 nmol/l after 5 months (Fig. 5). These groups are medium sized - a total of 22 patients, of which 13 had and 9 did not have supplementation.

In the group of patients who initially had normal vitamin D levels, children supplemented with cholecalciferol show an increase of vitamin D levels in the first month to 119 nmol/l, which stays the same after 3 months and then decreases a bit to 96 nmol/l. On the contrary, the levels of children without cholecalciferol decrease the whole time, getting close to deficit levels after 5 months - 55.3 nmol/l (Fig. 6). These groups are the smallest in size - a total of 10 patients, of which just 4 had and 6 did not have supplementation.

We can conclude that, in all the groups, even the small subgroups, the clear effect of vitamin D administration is visible on its levels, compared to non-supplemented patients.

In all groups (all Figures), we can also observe a trend of decreasing vitamin D levels in the later months of fracture healing. In non-supplemented patients, the decrease is noticeable in most groups the entire time, or from the 1st month of healing, but in some subgroups, we observe a slight decrease between the 3rd and 5th month even in supplemented children. We can therefore assume that fracture healing consumes vitamin D to such an extent that it is evident in its serum/plasma levels by a gradual decrease, as even in some supplemented patients a slight decrease is eventually evident (Figs 1-6).

From all examinations during the study period (n=278), normal levels of vitamin D were found in 32 % of the examinations. A vitamin D insufficiency was found in 40 %, and a deficit in 28 %, and these examinations were already influenced by the supplementation of some patients. Serum ALP activity was increased at least once during follow-up in 12 patients (11.2 %), decreased at least once in 7 children (6.5 %), while deviations in this level

could always be observed with a simultaneous rise (with increased ALP activity), or by a decrease (with reduced ALP activity) in serum concentrations of vitamin D3. An increase of parathormon was not detected in any patient.

At the first examination at the time of the injury (and therefore before the possible cholecalciferol supplementation), only 21.5 % patients had normal levels of vitamin D, 36.5 % had vitamin D insufficiency, and 42 % had a deficit. Let us remember that these were healthy children - according to the inclusion criteria - none of them were being treated for a disease that would predict a decrease in vitamin D levels.

In the literature, there are many studies in which adult patients are investigated, especially elderly people with osteoporosis: Gorter *et al.* pointed out the high frequency of vitamin D deficiency in adult fracture patients [7]. Eschle *et al.* found in their review of the literature mainly animal studies and human studies only in elderly patients with osteoporosis [8]. ESCEO working group concluded that 1000 IU daily should be recommended in patients at an increased risk of vitamin D deficiency [9]. Bodendorfer *et al.* supplemented vitamin D and calcium in adult patients treated with fractures and evaluated the frequency of complications and necessary reoperations. However, vitamin D levels were not statistically significantly different in patients with complications or necessary reoperation, compared to the group without, neither at the time of injury, nor during follow-up [10]. Ettehad *et al.* monitored 25-hydroxyvitamin D levels during healing of femoral or tibial diaphyseal fractures in adult patients. Blood tests were taken at the time of the injury, and again after one and three weeks. The levels decreased gradually. The authors attribute the decrease to the body's use of vitamin D for fracture healing and callus formation and consider whether it would be appropriate to supplement patients with vitamin D during fracture healing for that reason [11]. Doetsch *et al.* demonstrated a positive effect of calcium and vitamin D supplementation on the healing of the proximal humerus fractures in women with osteoporosis, when the callus grew significantly faster compared to the control group without supplementation [12].

In studies that already investigate the pediatric population: from the available reviews of the literature, it is evident that there is a lack of studies evaluating the effects of vitamin D on fracture healing, and their results are therefore difficult to evaluate. A study in which only vitamin D was supplemented was also not found. It was always in combination with calcium administration [13]. Cannell *et al.* warn against neglecting rickets and other diseases when multiple fractures and deformities are found on the skeleton and assigning this finding to the suspicion of CAN (child abuse and neglect) syndrome with all the consequences, including possible removal of the child from the parents [14], likewise Servaes *et al.* [15]. Taylor mentions the importance of vitamin D in association with rickets, but on the other hand lacks studies about the subject [16]. Maier *et al.* found a very high incidence of vitamin D deficiency in patients with osteochondritis dissecans and considered its correlation with the development of this disease [17]. Cheng *et al.* evaluated fractures in children with skeletal disease in congenital heart defects - 40 % of them had low levels of vitamin D [18]. McClellan *et al.* evaluated vitamin D levels and bone densitometry in adolescent patients with lumbar stress fractures of the pars interarticularis. In their group, they demonstrated a higher incidence of deficiency (13 %) and insufficiency (50 %). All these patients had normal bone density, and based on their results, the authors recommend routine examination of vitamin D levels in adolescents with these fractures, but not bone densitometry [19]. Wilsford *et al.* evaluated the incidence of vitamin D deficiency in patients with osteogenesis imperfecta and looked for risk factors where they demonstrated a statistically significantly higher incidence of vitamin D deficiency in older children, African Americans, or those with a higher BMI [20]. Parry *et al.* evaluated preoperative vitamin D levels in children undergoing elective orthopedic procedures - 90 % of these patients had vitamin D insufficiency, statistically significantly lower values were observed in African American children and patients examined in winter. Older patients often had the lowest levels. On the contrary, neither gender nor weight had a statistically significant effect [21].

Some studies have followed up on the connection between fractures and the saturation of the organism with vitamin D: according to the review by Moon *et al.* there is insufficient data in the literature to assess fracture risk rates in children in relation to vitamin D levels [22]. El-Sakka *et al.* present a set of Egyptian children 3-10 years old, where 32.6 % of them had vitamin D deficiency. Half of the children in the study had a forearm fracture, where 43.5 % had a vitamin D deficiency, the other half were the control group, where "only" 21.7 % had deficiency [23], Hosseinzadeh *et al.* describe high incidence of low vitamin D levels in patients with low energy forearm fractures, especially in obese children and in fractures requiring surgical treatment [24]. James *et al.* retrospectively

evaluated vitamin D levels in 181 pediatric patients treated for an upper extremity fracture. 35 % had normal levels of vitamin D, 41 % insufficiency, and 24 % vitamin D deficiency [25]. Clark *et al.* recommend examination of vitamin D in patients treated for skeletal injuries and its adequate supplementation, based on the literature and their own experience with a high incidence of vitamin D deficiency in children [26]. Ceroni *et al.* evaluated vitamin D levels in 100 adolescents with a limb fracture compared to 50 without one. Of the uninjured, 60 % had normal levels, 34 % insufficiency, and 6 % deficiency. Of the injured, 52 % had normal levels, 36 % insufficiency, and 12 % deficiency. They therefore pointed to low levels of vitamin D in the population of their adolescents but did not evaluate the further development of laboratory values, nor the healing of fractures [27]. Ryan *et al.* compared groups of African American children with and without forearm fractures (5-9 years). In their group, children with fractures were statistically significantly more likely to have vitamin D deficiency, lower bone density, and more often to be obese [28]. Thompson *et al.* prospectively compared the levels of vitamin D in a group of children with a fracture and a group without, where they demonstrated a statistically significantly higher incidence of low vitamin D levels in the group with a fracture [29]. Gorter *et al.* evaluated the incidence of vitamin D deficiency in children with fractures. The deficit had 34 % of the 187 patients. Of these patients, 74 % already had normal values after 4 months of supplementation. They rate older children, the spring season, and non-Caucasian skin type as risk factors [30]. Zheng *et al.* in their meta-analysis found no relationship between vitamin D level and the risk of bone fractures in children [31]. Contreras *et al.* prospectively assessed vitamin D levels in children with and without fracture. They found no statistically significant difference between the two groups. The median values for both groups were at the level of vitamin D insufficiency [32]. In Ireland, they found that 38 % of children with low energy fractures had a deficit of vitamin D [33]. Lee *et al.* compared the prevalence of vitamin D deficiency in children with fractures before and during the Covid-19 pandemic and they found even lower serum levels during the pandemic, especially in younger children [34].

Thus, in all these works, children were examined and followed, but unlike our study, they were not actively supplemented.

In some studies, the evaluation of bone mineral density is considered significant, whether together with or without the level of vitamin D: Boyce *et al.* offer recommendations for the diagnostics of children with fractures to differentiate traumatic and pathological fractures. In their opinion, it is necessary to combine densitometric examination (Z-score compared to age, sex, ethnicity) and laboratory examination (plasma levels of calcium, 25-hydroxyvitamin D, ...) [35]. Michalus *et al.* compared bone density in children with a history of multiple fractures versus a control group and demonstrated statistically significantly lower bone density values in children with multiple fractures. At the same time, these patients had a higher incidence of hypercalciuria, hypermagnesiuria, and hyperphosphaturia. Decreased vitamin D levels were observed in 25 % of children after multiple fractures compared to 19 % in the control group [36]. Ryan evaluated the increasing incidence of pediatric patients with forearm fractures and observed decreased bone density and sometimes lower calcium levels and obesity. In his work, he does not evaluate or describe the relationship to lower levels of vitamin D and genetic factors but assumes them [37].

Conclusion

In our study, all the patients supplemented with vitamin D3 had statistically significantly higher vitamin D levels already after one month of administration and they remained on normal vitamin D levels for the rest of the study period. Non-supplemented patients, on the other hand, had insufficient vitamin D levels for the whole study period, with a decrease over time. The similar trend can be observed when we divide children into subgroups, according to their fracture type or their initial vitamin D levels.

We also confirmed a high prevalence of insufficient vitamin D levels in the pediatric population in general at the time of their injuries.

In addition, we observed a trend of decreasing vitamin D levels during fracture healing - for the entire time in non-supplemented patients, but slightly in supplemented children as well during later months and we assume the consumption of vitamin D by fracture healing.

Therefore, based on our results, we recommend vitamin D testing for children healing with fractures (both at the time of the injury and after a fracture is healed) and administration of cholecalciferol for patients with lower levels. Studies investigating fracture healing compared with vitamin D levels are needed, as well as studies of patients with different fracture types.

Conflict of Interest

There is no conflict of interest.

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