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Medical Treatment of Bone Metabolism's Disorders among Patients with Vitamin-D Dependent Rickets Type 1

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Abstract

Aim: Determination the effects of medical therapy for genetically caused disorders of bone metabolism in patients with vitamin D-dependent rickets type 1.

Materials and Methods: In the consultative and out-patient department of State institution "Institute of Traumatology and Orthopedics National of the Ukrainian academy of medical sciences" we have examined and treated 48 patients with a diagnosis of VDDR-1. Medical treatment of these patients was carried out along the 4 stages. The 1st stage included a full examination of the patient including serum calcium, serum and urine phosphorus, determination of serum calcidiol and calcitriol, indices of parathyroid hormone and osteocalcin, as well as bone formation's marker P1NP and bone resorption's marker B-CTx. At the first stage, the children mandatorily were exposed to genetic test to detect changes (polymorphisms) in alleles of receptors to vitamin D (VDR) and type 1 collagen (COL1). The studies at the next stages were conducted completely, except for genetic research.

Results: Comprehensive study of vitamin D metabolism and biochemical indices of bone tissue viability among patients with VDDR-1 contributed to better understanding of some topics of pathogenesis and nature of osteomalation changes and subsequent osteoporotic alterations at different levels as well as to objectification of these changes in relevant biochemical indices and depending on changes to development if the different regimens of drug treatment in this disease.

Conclusion: For medical treatment of VDDR-1 alfacalcidol is the drug of choice because it has the ability to be transformed by the liver into calcitriol, avoiding genetically affected renal 1α hydroxylation.

Taking into account bio chemical indices among patients with VDDR-1we have developed pathogenesis-oriented effective drug therapy of orthopedic manifestations that includes (80,000 IU/month) and alfacalcidol (7.5 mg/month). The offered treatment provides significant improvement in bone metabolism represented in biochemical and clinical parameters after the first month of three-month stage of treatment ($p<0.05$).

Keywords: Vitamin D-dependent rickets; Rickets; Vitamin D metabolism; Calcidiol; Lower extremities' deformities in children

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Introduction

Vitamin-D-Dependent Rickets (VDDR) or hereditary rickets is a genetically determined disease associated with impaired Vitamin D (VD) metabolism. It is divided into two types. In VDDR-1 the conversion of 25-hydroxy vitamin D to 1, 25-dihydroxy vitamin D does not occur or is partially inhibited [1]. This breakdown develops due to deficiency or anomaly of renal 1,25-hydroxylase, that is necessary for the conversion of 25-hydroxy vitamin D into 1,25-dihydroxyvitamin D [2-4]. VDDR-2 represents a terminal organ's insensitivity to the autogen of 1,25-dihydroxyvitamin D [5,6].

There are many different causes of rickets (osteomalacial) syndromes, but all of them lead to the lack of available calcium and phosphorus to mineralize the newly formed osteoid. Because these disorders have a common direction (defects in bone mineralization), children with rickets and rickets-like diseases have a very similar clinical picture. This stereotype prompts the physician along with clinical or radiological tests to use widely sophisticated laboratory studies to clarify the nature of bone metabolism disorders. Some of them have become available only recently [7-13]. Data on bone metabolism, received by us [1], made it possible to treat bone metabolism disorders in

VDDR-1 with biochemical control and the conducted treatment was grounded upon the data on pathogenesis of the disease.

The aim of the study was to determine the effect of drug therapy upon genetically caused disorders of bone metabolism among patients with vitamin D-dependent rickets type 1.

Materials and Methods

In the consultative and out-patient department of State institution "Institute of Traumatology and Orthopedics National of the Ukrainian academy of medical sciences" 48 patients with diagnosis VDDR-1 were examined and treated. Boys constituted 54.17% of the patients, girls-45.83%. The majority of patients (70.83%) were referred at the age 1-2 years that coincided with the progression of orthopedic manifestations.

Medical treatment of patients with rickets-like disorders was performed along 4 stages. The 1st stage included a full examination of the patient including serum calcium, serum and urine phosphorus, determination of serum calcidiol and calcitriol, indices of parathyroid hormone and osteocalcin, as well as bone formation's marker P1NP and osteo-resorbtion's marker B-CTx. At the first stage, the children mandatorily were exposed to genetic test to detect changes (polymorphisms) in alleles of receptors to vitamin D (VDR) and type 1 collagen (COL1). The studies at the next stages were conducted completely, except for genetic research.

Distribution of the treated patients is presented in Table 1. Given that the blood test data are long-lasting and some of the assays have been sent to commercial laboratories outside Ukraine, the inter-examinations time at the different therapeutic stages ranged between 3 to 3.5 months.

As one can see in the table 1, not all patients underwent all the planned stages of examination and treatment, which is associated with the positive clinical effect already at the first stages of pathogenetically grounded therapeutic measures.

Results and Discussion

The treatment was performed with vitamin D (Aquadetrim®, Vigantol®), precursor to the active metabolite of vitamin D-alfacalcidol (Alpha-D3®-Teva), and calcium (Figure 1).

The treatment of orthopedic manifestations of VDDR-1 started with 80,000 IU of vitamin D, 7.5 μg of alfacalcidol and 15 g of calcium per month. In 3 months of treatment a re-examination of bone metabolism was performed, resulting in diminution in dose - about 60,000 IU of vitamin D and 5 μg of alfacalcidol. The children consumed calcium at a daily dose 500 mg without correction.

At the 3rd stage of treatment the dose of vitamin D remained at the same level, and we tried to reduce the amount of alpha-D3®-Teva down to 3 μg per month, but subsequently, as it is shown in the graph from the Figure 1 and 2, we finally returned to the dose of alfacalcidol 5 μg due to the deterioration of bone metabolism parameters.

Let us consider now how blood and urine indices changed during the correction of bone metabolism among patients with VDDR-1 during pathogenetically grounded treatment.

As one can see in the Table 2, after the first stage of treatment, blood parameters significantly improved, while the study of urinary minerals' excretion did not display a significant difference.

Already at the first stage of treatment we observed a significant

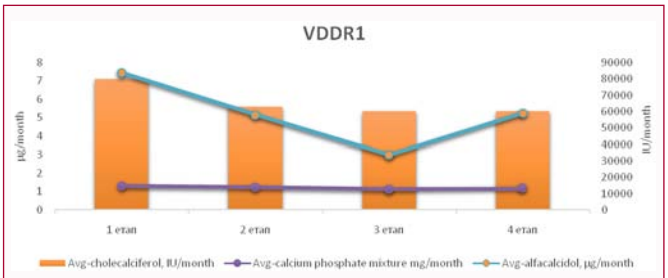

Figure 1: Schematic representation of the average monthly dose of drugs used to treat patients with VDDR-1.

Table 1: Number of treated patients depending on the nosology and stage of treatment.

Diagnosis	Stages of treatment			
	Stage 1	Stage 2	Stage 3	Stage 4
VDDR-1	48	21	4	2

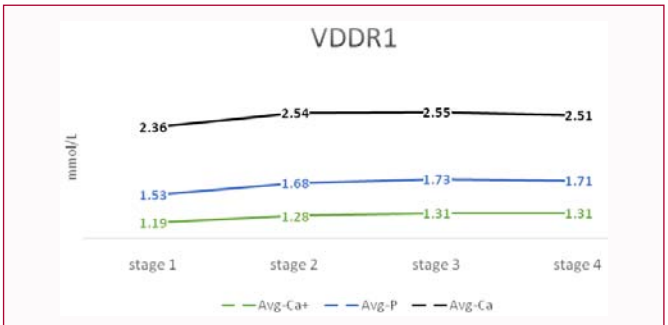

Figure 2: Graphic representation of calcium and phosphorus indicesduring the treatment.

increase of blood calcidiol and calcitriol, subsequently the level of calcidiol was in the upper age-related normal limit, and calcitriol displayed some fluctuations (Figure 3). The therapeutic effect, in particular, alignment of lower extremities' deformities, was observed already after the 2nd stage of treatment.

In our studies, we observed a significant decrease of the level of parathyroid hormone already at the first stage of treatment. The marker of bone metabolism reacted less strongly, although a clear tendency to its normalization was observed.

Bone formation and resorption were normalized after initiation of treatment. As one can see in the Figure 4, parameters of P1NP and B-CTx display steady regression, which in turn significantly slows down bone metabolism, allowing bone tissue to mature completely.

Renal calcium reabsorption was almost unchanged; daily urine calcium levels were below normal, there by contributing to its accumulation in bloodstream (Figure 5). Urine phosphorus increased slightly after the 3rd stage of treatment, although it remained within normal range too (Figure 5).

Interesting results were obtained while studying correlations at the first stage of treatment. It was revealed, that with adequate (pathogenetic) therapy an increase and strengthening of correlations become evident. This statement can be clearly substantiated in Figure 6 (pre-treatment) and Figure 7 (after the first stage of treatment). Due to the lack of patients in treatment groups 3 and 4, correlation links between blood and urine indices were not calculated.

A comprehensive study of vitamin D metabolism and

Table 2: Indices of bone metabolism at the stages of treatment of patients with VDDR-1.

Indices of bone metabolism/stages of treatment	Stage 1 M ± m	Stage 2 M ± m	Stage 3 M ± m	Stage 4 M ± m
Calcium (ionized)	1.19 ± 0.01	1.28* ± 0.01	1.31* ± 0.02	1.31* ± 0.01
Phosphorus (blood)	1.53 ± 0.03	1.68* ± 0.03	1.73* ± 0.04	1.71 ± 0.04
Calcium (total)	2.36 ± 0.03	2.54* ± 0.03	2.55 ± 0.02	2.51 ± 0.00
Calcidiol	30.94 ± 2.29	66.47* ± 6.44	53.84* ± 8.92	61.22* ± 28.79
Calcitriol	60.71 ± 2.62	154.86* ± 17.69	228.50*± 46.30	196.50* ± 38.50
Parathormone (intact)	72.85 ± 9.68	26.07* ± 1.68	26.875 ± 7.00	27.72 ± 1.12
Osteocalcin	78.69 ± 6.45	49.78* ± 6.15	32.60* ± 20.68	57.795 ± 12.80
Urinecalcium (daily)	1.42 ± 0.06	1.24 ± 0.10	2.00*# ± 0.28	1.85 ± 0.35
Urinephosphorus (daily)	7.84 ± 0.44	7.33 ± 0.79	73.725 ± 2.13	11.45** ± 0.45
P1NP	1037.63 ± 26.20	712.71* ± 39.83	561.50* ± 94.29	585.60* ± 21.50
B-CTx	1.68 ± 0.06	1.46* ± 0.07	1.685 ± 0.11	1.345 ± 0.45

* - significance of inter-parameters differences comparing to the 1st stage of treatment, p<0.05
** - close trend to significance of inter-parameters differences comparing to the 1st stage of treatment, 0, 1> p>0.05
# - significance of inter-parameters differences comparing to the 2nd stage of treatment, p<0.05

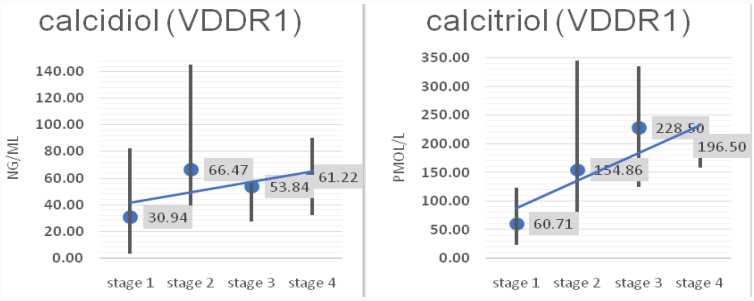

Figure 3: Graphical representation of the calcidiol and calcitriol indices during the treatment.

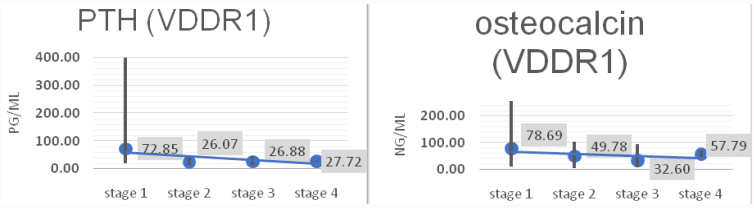

Figure 4: Graphical representation of bone formation's and resorption's indices during the treatment (ng/ml).

biochemical indices of bone tissue's viability among patients with VDDR-1has allowed us to deepen our understanding of some issues in the pathogenesis and nature of osteomalacia and subsequent osteoporotic changes at the different degrees, to objectify these alterations in the relevant biochemical indices and, depending on the changes, to develop different regimens of pharmacological correction in this disease.

Thus, in the early reports on treatment of 1α-hydroxylase deficiency, large doses (50,000-200,000 IU) of vitamin D2 were administered daily, that was associated with clinical changes, biochemical and radiographic alterations and improvements of growth speed [5,9,10,13,].

Hypocalcaemia and hyperparathyroidism, in turn, have been treated with 1 αOND3 in the dose 1-3 ug/day (80 to 100 ng/kg). 1 α-hydroxyD3 is an analogue of vitamin D that requires 25-hydroxylation in liver. The synthetic analogue of dihydrotachysterol (DHT) is not 1 α-hydroxylated, but contains a hydroxyl group in the 3-α position; an A-ring rotation with close 6-7 carbon link brings this group into a pseudo-1 α-hydroxyl configuration, so that DHT is active without 1 α-hydroxylation [8].

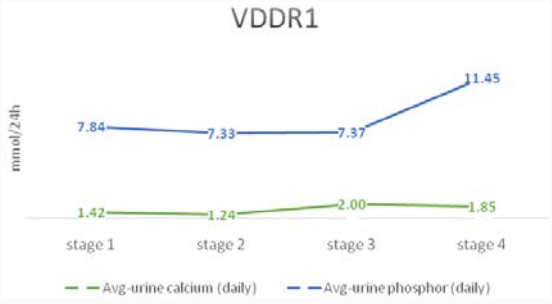

Figure 5: Graphic representation of calcium and phosphorus renal excretion during treatment.

Ukrainian analogue is the drug alfacalcidol (1 α $(OH)_2D_3$), that in contrast to complete calcitriol must undergo 25-hydroxylation in liver and obtain the calcitriol formula - $1.25(OH)_2D_3$ (i.e. it requires

Correlations (marc vdzr1.sta)
Marked correlations are significant at p <,05000
N=48 (Casewise deletion of missing data)

	Ca+	P	Ca	25(OH)D	1,25(OH)2D	PTH	osteocalcin	urine calcium (daily)	urine phosphor (daily)	P1NP	B-CTx
Ca+	1,00	0,32	0,35	0,12	0,29	0,05	-0,09	0,19	0,39	0,16	-0,03
P	0,32	1,00	0,35	0,16	0,35	-0,35	-0,40	0,27	0,40	-0,02	-0,09
Ca	0,35	0,35	1,00	0,08	0,21	-0,17	-0,27	0,13	0,06	-0,13	-0,22
25(OH)D	0,12	0,16	0,08	1,00	0,49	-0,42	-0,06	0,12	0,27	-0,20	-0,15
1,25(OH)2D	0,29	0,35	0,21	0,49	1,00	-0,13	-0,23	0,32	0,26	-0,16	-0,26
PTH	0,05	-0,35	-0,17	-0,42	-0,13	1,00	-0,04	-0,27	-0,17	0,01	-0,01
osteocalcin	-0,09	-0,40	-0,27	-0,06	-0,23	-0,04	1,00	-0,04	0,03	-0,01	0,47
urine calcium (daily)	0,19	0,27	0,13	0,12	0,32	-0,27	-0,04	1,00	0,37	0,01	-0,03
urine phosphor (daily)	0,39	0,40	0,06	0,27	0,26	-0,17	0,03	0,37	1,00	-0,01	0,12
P1NP	0,16	-0,02	-0,13	-0,20	-0,16	0,01	-0,01	0,01	-0,01	1,00	-0,03
B-CTx	-0,03	-0,09	-0,22	-0,15	-0,26	-0,01	0,47	-0,03	0,12	-0,03	1,00

Figure 6: Schematic representation of correlations between blood and urine indices in patients with VDDR1 (pre-treatment).

Correlations (marc vdzr1.sta)
Marked correlations are significant at p <,05000
N=21 (Casewise deletion of missing data)

	Ca+	P	Ca	25(OH)D	1,25(OH)2D	PTH	osteocalcin	urine calcium (daily)	urine phosphor (daily)	P1NP	B-CTx
Ca+	1,00	0,35	0,42	0,37	0,53	-0,28	-0,26	0,19	-0,20	0,26	0,12
P	0,35	1,00	0,28	0,33	0,15	-0,54	-0,62	-0,25	0,12	-0,06	0,16
Ca	0,42	0,28	1,00	-0,07	0,39	0,01	-0,60	-0,31	-0,02	-0,16	0,11
25(OH)D	0,37	0,33	-0,07	1,00	0,33	-0,32	-0,17	-0,07	-0,18	0,20	-0,31
1,25(OH)2D	0,53	0,15	0,39	0,33	1,00	-0,14	-0,25	-0,23	0,22	0,44	0,11
PTH	-0,28	-0,54	0,01	-0,32	-0,14	1,00	0,45	0,08	-0,08	0,11	0,12
osteocalcin	-0,26	-0,62	-0,60	-0,17	-0,25	0,45	1,00	0,54	0,04	0,41	-0,22
urine calcium (daily)	0,19	-0,25	-0,31	-0,07	-0,23	0,08	0,54	1,00	-0,25	0,29	0,10
urine phosphor (daily)	-0,20	0,12	-0,02	-0,18	0,22	-0,08	0,04	-0,25	1,00	0,00	0,05
P1NP	0,26	-0,06	-0,16	0,20	0,44	0,11	0,41	0,29	0,00	1,00	0,20
B-CTx	0,12	0,16	0,11	-0,31	0,11	0,12	-0,22	0,10	0,05	0,20	1,00

Figure 7: Schematic representation of correlations between blood and urine indices in patients with VDDR1 (after the first stage of treatment).

no 1 α-hydroxylation).

Thus, study of biochemical parameters among patients with vitamin-D-dependent rickets type 1 and developed pathogenetically-grounded effective drug therapy of disease's orthopedic manifestations, including cholecalciferol (80000 IU/month) and alfacalcidol (7.5 μg/month), had led to significant improvement in bone metabolism, that was reflected in biochemical and clinical parameters after the first month of three months stage of treatment ($p<0.05$).

This therapy can be used as an independent approach and aimed at improvement of bone tissue's metabolism and structural and functional state; also it can be administered in the pre- and postoperative periods among patients undergoing surgical correction of multi-planed bone deformities.

The purpose of the therapy developed and applied by us was to achieve a significant reduction of bone deformities, improvement of bone structure, betterment of activity in growth areas of the child's body. This treatment was used as mono therapy that mostly led to medication-induced alignment of the multi-planed bone deformities of the lower extremities, and combined with operative corrections of these deformities using a minimally invasive method (hemiepiphysiodesis) or operations with usage of growing intramedullary constructs.

Conclusions

For drug treatment of VDDR-1alfacalcidol is the drug of choice because it has the ability to be transformed in liver into calcitriol bypassing genetically affected renal 1α hydroxylation.

Based upon the study of biochemical parameters among the patients with vitamin D-dependent rickets type 1 we have developed a pathogenetically-grounded effective drug therapy of orthopedic manifestations that included cholecalciferol (80000 IU/month) and alfacalcidol (7.5 μg/month). The offered treatment provides a significant improvement in bone tissue metabolism that is reflected in biochemical and clinical parameters after the first three months stage of treatment ($p<0.05$).

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