ORIGINAL ARTICLE

IMPROVEMENT OF ERADICATION THERAPY IN CHILDREN WITH DUODENAL ULCER ASSOCIATED WITH *HELICOBACTER PYLORI*

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ABSTRACT

The aim: To evaluate the efficacy of the drug VitD children with *H.pylori*-associated duodenal ulcer.

Materials and methods: Two treatment groups of children with DU were formed: I - 60 children with *H. pylori*-associated DU, who received the optimal scheme of anti-Helicobacter therapy (AHBT) for Chernivtsi region; II - 62 children with *H. pylori*-associated DU who received a modified treatment regimen: AGBT + VitD at a dose of 2000 IU / day for 1 month. The effectiveness of the treatment was evaluated taking into account the Relative Risk Reduction (RRR) of the adverse event and Number Needed to Treat (NNT).

Results: All children with DU and a positive *H. pylori* infection test showed changes in serum VitD levels: 81.9% deficiency and 18.1% insufficiency. Successful eradication was achieved in 77.1% of children, in particular in the first group 73.3%, in the second - 82.2%. Predictors of successful eradication are the duration of infection, *H. pylori* CagA (+), VitD level. When using the VitD treatment regimen in children with DU associated with CagA (+) strain *H.pylori*, RRR was observed 2.29 times ($\chi 2 = 6.34$, $p\varphi < 0.05$) with NNT 1.59.

Conclusions: Due to the reduced level of serum VitD in children with *H. pylori*-associated DU, it is advisable to include in the treatment regimen the adjuvant component of AHBT in the form of VitD. Predictors of effective eradication of *H. pylori* are CagA (+) strain of *H. pylori*, duration of infection and VitD level.

KEY WORDS: Keywords: children, *H. pylori*, duodenal ulcer, vitamin D, eradication therapy

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INTRODUCTION

Vitamin D (VitD) is an indispensable for the human body organic compound with high biological activity, which has recently received increased attention from scientists around the world [1, 2]. This is due to the fact that in recent years its metabolism, functions and effects on the human body have been deeply studied (Fig. 1).

With the help of specific metabolic processes in the human body, VitD is converted into a highly active hormonal form. VitD receptor proteins have been identified in skin, heart, lung, brain, skeletal muscle, colon, stomach, placenta, breast, pancreas, and endocrine cells [3]. VitD receptors (Fig. 2) are also present on activated CD4+ and CD8+ T-lymphocytes, B-lymphocytes, neutrophils, macrophages, dendritic cells [4].

Many studies have shown that a deficiency of VitD metabolites causes the development of somatic diseases such as diabetes of both types [5], cardiovascular disease [6], multiple sclerosis [7], psoriasis [8], diseases of the digestive system [9], kidneys [10] and other organs and systems due to pleiotropic action [11].

The relationship between vitamin D and *Helicobacter pylori* infection (*H. pylori*) is currently being considered [12]. *H. pylori* is a clinically significant pathogen responsible for a significant proportion of overall morbidity and mortality worldwide [13]. The range of *H. pylori*-related diseases is constantly expanding. *H. pylori* causes 60-90% of gastric and 95% of duodenal ulcers, 80% of cases of chronic gastritis (type B), 60% of cases of gastric cancer [14]. The most severe course and possibility of complications in children is duodenal ulcer (DU), which in 90% of cases is associated with *H. pylori*. The prevalence of colonization varies between children and adults. The global *H. pylori* prevalence in children varies significantly, from 2.5% in Japan [15] to 34.6% in Africa [16]. According to 44 studies, the prevalence of *H. pylori* in Europe ranged from 17% (Denmark) to 88% (Russia) [17]. In recent years, studies have shown a decrease in the prevalence of *H. pylori* [18-20]. However, in Ukraine the frequency of detection of *H. pylori* among children with gastroduodenal pathology is high and is 67.2% [21]. More than 25 years of experience in the treatment of *H. pylori* infection has shown that eradication is becoming an increasingly difficult task, as the microorganism quickly becomes resistant to antibacterial drugs. The immune response of the macroorganism is a determining factor in the clinical manifestation of the pathogenic properties of *H. pylori*. Today, the role of VitD in the body's immunoregulatory responses to infectious agents, in particular *H. pylori*, is being actively considered. VitD deficiency manifests itself in the form of increased proinflammatory vector of congenital and adaptive immune responses, which reduces the effectiveness of eradication of *H.pylori* infection in infected patients [22].

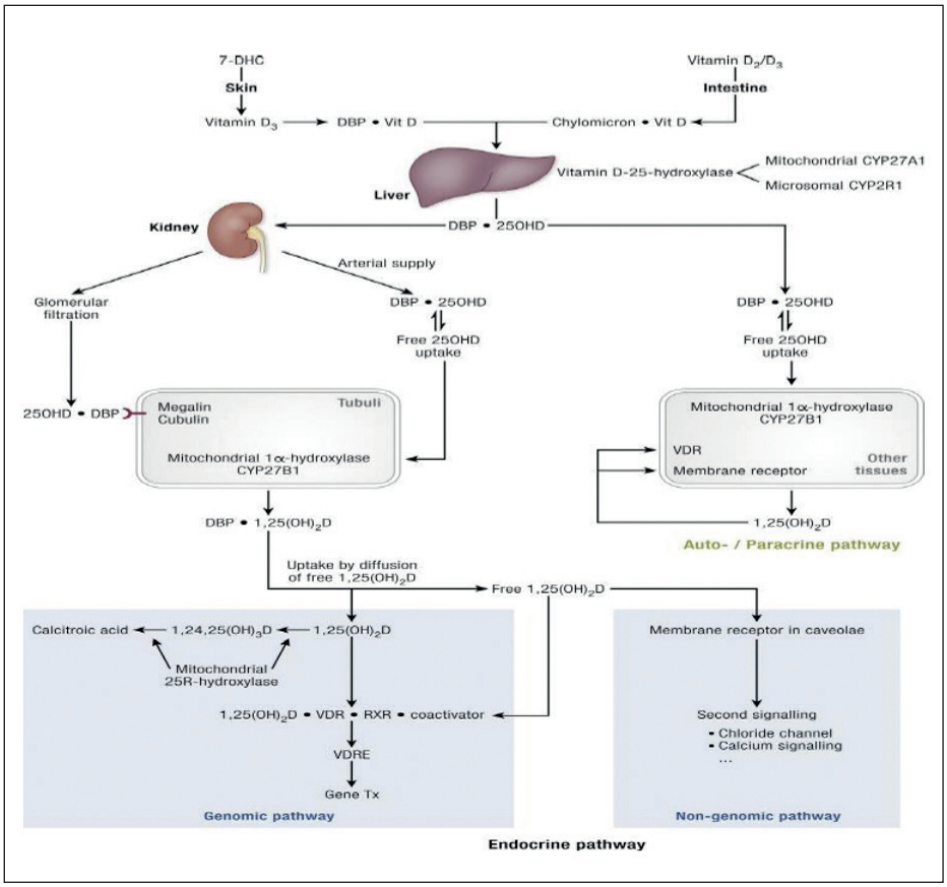

Fig.1. Metabolism and action of vitamin D [2].

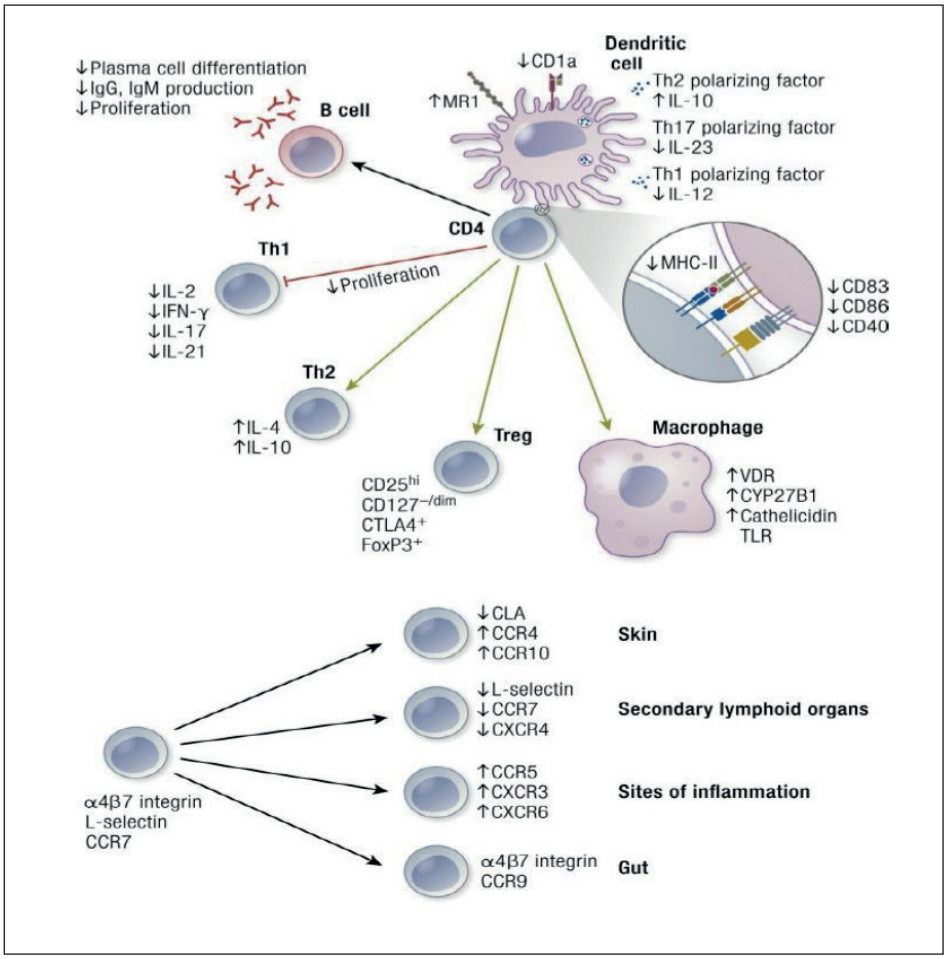

Fig.2. Vitamin D metabolism and signaling in the acquired immune system [2].

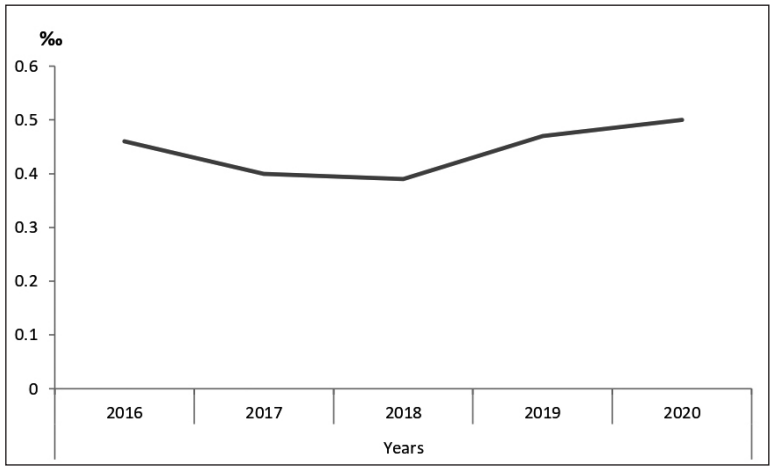

Fig .3. Prevalence of DU among children of Chernivtsi region

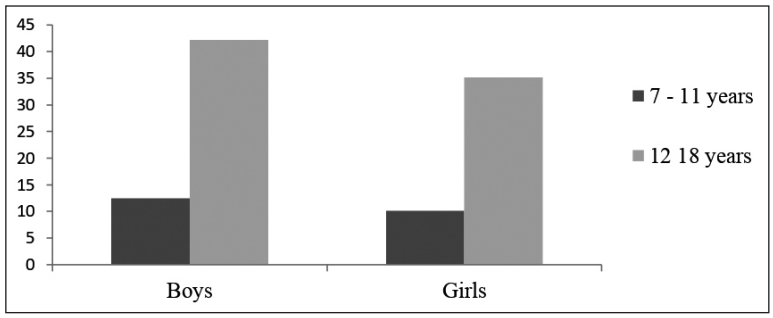

Fig 4. The frequency of DU in children depending on age and sex

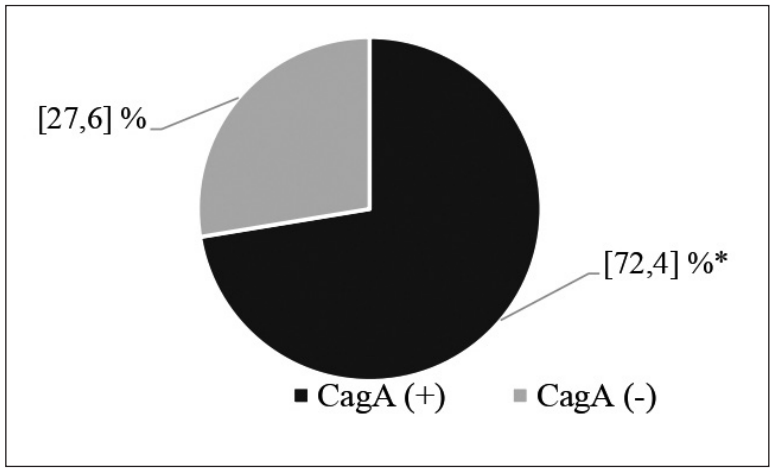

Fig 5. The frequency of infection with CagA strain *H. pylori*. Note. * - probably for children with CagA (-), p <0.05.

THE AIM

The aim was to evaluate the effectiveness of VitD in children with *H.pylori*-associated DU.

MATERIALS AND METHODS

During the period 2016-2020, a survey of 135 children with DU aged 7-18 years, who were hospitalized in the gastroenterology department of the Chernivtsi Regional Children's Hospital, was conducted. The control group consisted of 30 healthy children of the previously specified age (14 boys and 16 girls). The examinations of children were carried out in accordance with the principles of the Declaration of Human Rights of Helsinki, the Council of Europe Convention on Human Rights and Biomedicine and the relevant laws of Ukraine. In each case, informed consent was obtained from children and parents for clinical observations. These observations were authorized by the Bioethics Commission of Bukovynian State Medical University (protocol № 9 of 17.09.2016). The diagnosis of DU was verified in accordance with the order of the Ministry of Health of Ukraine №59 of 29.01.2013 [23] and the Roman criteria V [24]. A thorough paraclinical study was performed according to generally accepted methods in the clinic - general blood test, biochemical blood parameters, blood sugar test, general urine test, fecal analysis for helminth eggs, coprogram, study of intestinal microflora.

Using a fibrogastroduodenoscope "Pentax FG - 24P" performed endoscopic examination at the beginning of treatment to verify the diagnosis according to the "Sydney system" (1990), taking into account the peculiarities of this study in children (Doletsky S.Ya., 1984) and after 4-6 weeks

Table I. Distribution of examined children with DU depending on the provision of vitamin D and the method of treatment.

AHBT			AHBT +VitD			Control group		
I, n=60			II, n=62			n=30		
VitD N	VitD D	VitDIS	VitD N	VitD D	VitD IS	VitD N	VitD IS	VitD D
-	10	50	-	12	50	25	5	0

Notes:VitD N - vitamin D normal (vitamin D level of30-100 ng/mL); VitD D- vitamin D deficient (vitamin D level of <20 ng/mL); VitD IS- vitamin D insufficient (vitamin D level of 21-29 ng/ mL); anti-Helicobacter therapy, AHBT.

Table II. Morphological signs of DU in children depending on the level of vitamin D.

Indicator of morphological changes	VitD IS (n = 91), abs ./%	VitD D (n = 2 2), abs ./%
The severity of chronic inflammation		
1st degree	11/12,1	7/31,8*
2nd degree	27/29,7	12/54,5*
3rd degree	53/58,2	3/13,6**
Inflammatory activity		
1st degree	2/2,1	5/22,7*
2nd degree	34/34,3	16/72,7*
3rd degree	61/61,6	1/4,5**
Atrophy	2/2,1	0
Intestinal metaplasia	0	0

Notes. Probable difference * - (pφ<0,05); ** - (pφ<0.01). Note. VitD D- vitamin D deficient; VitD IS- vitamin D insufficient.

Table III. Indicators of *H. pylori* eradication in the examined children

Group	Treatment scheme	Successful eradication	
		Abs.	%
Group I (n=60)	AHBT	44	73,3
VitD IS (n=50)		38	76,0
VitD D (n=10)		6	60,0
Group II (n=62)	AHBT + vitamin D	51	82,2
VitD IS (n=50)		42	84,0
VitD D (n=12)		9	75,0

Notes. VitD D - VitD deficient; VitD IS - VitD insufficient; AHBT - anti-Helicobacter therapy.

after treatment (eradication control). Biopsies were taken directly from the body, the antrum of the stomach, and the bulb of the duodenum during endoscopic examination (Sydney-Houston system, 1996). Matrix smears of gastric mucosa and duodenum after fixation and drying in air for 10 minutes were stained with azure-eosin. The drugs were studied under oil immersion with an increase of x 630. *H. pylori* was visualized as a curved or helical bacterium. A rapid urease test (URE-HP test, PLIVA-Lachema, Czech Republic) was performed to test biopsies for *H. pylori* infection and a "HelicoBest-antibody" diagnostic test system (seriesD-3752) was used to detect specific immunoglobulins of classes M, A and G to the antigen CagA *H. pylori* in serum by enzyme-linked immunosorbent assay (ELISA), which was performed according to the conventional method using a set of reagents from the company "Vector BEST" (Russia). The results were evaluated using a spectrophotometer, measuring the optical density at a wavelength of 450 nm. *CagA* antibody titers (≥8 U/mL) were classified as positive, per manufacturer instructions. The patient was considered to be cured of *H. pylori* infection if all tests were negative.

After the eradication course, the presence of *H. pylori CagA* antigen in the feces was determined by ELISA according to the conventional method using a set of reagents from "Farmasco" (Sweden). Studies of acid-forming function of the stomach were performed on all examined children by intragastric pH-metry according to the method of V.M. Chornobrov on the acidogastrograph AG-1pH-M №139 (Ukraine). The study was performed in the morning (until 10.00) on an empty stomach with oral administration and removal of the pH microprobe in compliance with the necessary rules of preparation for probe examination methods.

Table IV. Terms of disappearance of the main clinical syndromes in children with DUafter treatment

Groups of children	Term of disappearance of clinical syndromes (M ± m), days		
	painful	dyspeptic	asthenovegetative
I (n=60) VitD IS (n=50) VitD D (n=10)	7,2 ± 0,3	5,9 ± 0,2	5,8 ± 0,1
	6,8 ± 0,2	4,8 ± 0,3	6,1 ± 0,2
	7,3 ± 0,1	5,3 ± 0,4	6,8 ± 0,1
II (n=62) VitD IS (n=50) VitD D (n=10)	4,3 ± 0,4*	4,4 ± 0,2*	4,6 ± 0,1*
	5,1 ± 0,4*	4,5 ± 0,4	5,3 ± 0,2*
	6,1 ± 0,3*	5,1 ± 0,3	6,4 ± 0,2

Notes. * - p<0,05. VitD D - VitD deficient; VitD IS - VitD insufficient.

Table V. Evaluation of the effectiveness of complex therapy in children with DU

Treatment scheme	RRR (95% CI)	NNT	TS,% (95% CI)	TP,% (95% CI)
Protocol therapy with the inclusion of VitD	2,29 (0,18-5,43)	1,59	75,44 (57,05-90,17)	89,09 (66,09-97,62)

Notes. RRR - reduction of relative risk; NNT - number need ttreated; TS - test sensitivity, TP - test peculiarity, CI - confidence interval.

Serum 25(OH)D3 levels were measured using an electrochemiluminescence method (Roche Diagnostics GmBH, Mannheim, Germany), with inter-assay and intra-assay coefficients of variation (CVs) of 2.4% and 5.7%, respectively. Sera obtained by centrifugation were stored at -20°C and analyzed simultaneously by technicians who were blind to group allocation. The results were evaluated according to the recommendations of the International Society of Endocrinologists (Holick MF, 2011): VitD deficiency - 25(OH) D less than 20 ng/ml (less than 50 nmol/l); VitD deficiency - 25(OH)D 21-29 ng/ml (51-75 nmol/l); the normal content of VitD - 25(OH)D 30-100 ng/ml (76-250 nmol/l).

Before beginning *H.pylori* treatment patients were divided into 2 groups as follows: group 1 (VitD deficient, VitD D) had a VitD level of <20 ng/mL, and group 2 (VitD insufficient, VitD IS) had a VitD level of ≥20 ng/ mL.

Criteria for children's inclusion to the study:
- verified DU, associated with *H. pylori*;
- age of patients from 7 to 18 years;
- informational consent of parents and patients to conduct the planned examination.

Criteria for children's exclusion from the study:
-DU negative test for *H. pylori* and the presence of complications of DU;
- the presence of concomitant pathology (chronic pancreatitis, chronic cholecystitis, chronic hepatitis) and diseases that may affect the level of VitD in the serum (hyperthyroidism, malabsorption, rickets, hypercorticism, severe liver disease, kidney disease);
- age of the child up to 7 years;
- children treated with antibacterial agents over the last 6 month;
- children who have received systemic glucocorticoid therapy for more than 14 days in the last three months;
- non-signedinformational consent of parents and patients to conduct the planned examination;
- hypersensitivity to drugs proposed in the treatment regimen.

Criteria for children'swithdrawal from the study:
- decision of patient and parents to stop their participation in research;
- non-compliance during diagnosis and treatment;
- the emergence of exclusion criteria in the study process.

Two treatment groups were formed: I - 60 children with *H. pylori*-associated DU, who received the optimal scheme of anti-Helicobacter therapy (AHBT) for Chernivtsi region: bismuth preparation (4-8 mg/kg/day) + nifuratel (15 mg/kg/day) + amoxicillin (25 mg/kg/day) for 7-10-14 days; in case of increased gastric acid-producing function, famotidine (1-2 mg/kg/day) was added to children under 12 years of age, and esomeprazole (0.5-0.8 mg/kg/day) after 12 years of age; II - 62 children with *H. pylori*-associated DU who received a modified treatment regimen: AHBT + VitD at a dose of 2000 IU/day for 1 month.

Tolerability was assessed on a 4-point scale based on objective symptoms and subjective sensations reported by the patient during treatment. The condition of patients was assessed at the time of treatment, on day 10-14 of treatment, for 4 weeks after eradication therapy. Comparative evaluation of the effectiveness of different treatments was performed on the basis of analysis of the time of reduction of the main symptoms of the disease, the disappearance of signs of inflammation of the gastric mucosa/duodenum, the calculation of epidemiological indicators of treatment effectiveness.

The obtained results were analyzed using computer packages Statistica 6.0 StatSoft Inc. and Excel XP for Windows. Under the conditions of normal distribution of values (Shapiro-Wilk criterion> 0.05), parametric statistical methods were used to calculate the arithmetic mean (M) and the error of representativeness of the mean (m). The comparison of quantitative indicators with the

normal distribution was performed using Student's t-test. The comparison of relative values was performed using the exact Fisher criterion. Analysis of qualitative characteristics was performed according to criterion χ^2, at frequencies less than 5 - used the exact Fisher test. Differences were considered significant at $p<0.05$. The effectiveness of treatment was evaluated taking into account the reduction of the relative risk of adverse events (RRR), taking into account the minimum number of patients who need to be treated to obtain 1 positive result (NNT).

RESULTS

According to the Center for Statistics of the Ministry of Health of Ukraine, the prevalence of digestive diseases (2016-2017) among children in Ukraine averaged 115.48‰, the range of fluctuations ranged from 120.13‰ in 2016 to 111.74‰ in 2019, in Chernivtsi region there is a tendency to a gradual increase from 120.32‰ in 2016 to 163.26‰ in 2019 (average value - 132.58‰). In the population of children of Chernivtsi region, the average incidence in the age group 12-18 years was almost 1.4 times higher than in the group 7-11 years. The prevalence of DU during 2016-2020 ranged from 0.69 to 0.79‰ (Fig. 3).

The obtained data confirm the facts of the scientific literature on the cyclic course of DU due to the accumulation of determining predictors. Figure 4 shows the frequency of DU depending on age and sex.

DU was more common in children aged 12-18 years and in boys. In children of group I VitD insufficiency occurred in 83.3%, deficiency - in 16.7%, while in children of group II VitD insufficiency occurred in 80.6%, deficiency - in 19.3%. The distribution of children depending on the method of treatment and the level of vitamin D in the peripheral blood is shown in table I.

The total infection of the surveyed children with *H. pylori* was 90.4% (122 children out of 135 surveyed). Because one of the inclusion criteria was DU associated with *H. pylori*, 13 children were excluded from the study. The cytotoxic strain of *CagA H. pylori* was found in the vast majority of examined children with a positive test for *H. pylori* (Fig. 5).

Endoscopic examination showed that the nature of inflammatory changes of the mucous membrane in children in general was the same with the predominance of erythematous-exudative lesions, moderate activity of the inflammatory process, hyperacidity, but the most striking endoscopic picture was observed in children with frequent recurrences of the disease. in the lesion of the cytotoxic strain of *CagA H. pylori.* Morphological study of biopsies of the mucous membrane of children with DU on a visual-analog scale of semi-quantitative assessment of morphological changes according to M.F. Dixon (1996) are presented in table II.

The average level of serum VitD (25(OH)D) in children of group I was 22.9±3.1 ng/mL, group II - 21.6±3.1 ng/mL, and in healthy children - 38.7±4.8 ng/mL, $p<0.05$. All children with DU and a positive *H. pylori* infection test showed changes in serum VitD levels: 81.9% deficiency and 18.1% deficiency.

The results of the effectiveness of AHBT in children with DU in groups I and II are shown in Table III. The rate of successful eradication in the examined children of groups I and II was 77.1% (94 of 122 children).

That is, the inclusion of an adjuvant component in the form of VitD in children with insufficient supply or deficiency of VitD increases the effectiveness of AHBT.

We analyzed the rate of successful eradication in group II depending on the duration of *H. pylori* infection and found that the highest rate (96.2%) was in children with *H. pylori* infection before 1 year, in children 1-3 years of infection and with infection over 3 years - 17.4% and 20% respectively. The high efficiency of AHBT in children with a duration of infection up to 1 year indicates that the short history of *H. pylori* infection is one of the predictors of successful eradication. In 37 (92.5%) of 40 children of group II with the status of *H. pylori CagA (+)* eradication was successful in contrast to 10 (50%) children out of 20 with the status of *H. pylori CagA* (-). Thus, children with *H. pylori CagA (-)* status have a low rate of successful eradication, and *H. pylori CagA (-)* status may be an additional predictor of ineffective AHBT.

Analysis of the reduction of clinical symptoms of DU revealed a faster leveling of pain, dyspeptic and asthenovegetative syndromes in children of group II (Table IV).

Therefore, the inclusion of VitD in the standard protocol treatment contributes to better normalization of clinical and paraclinical changes, which is confirmed by indicators of epidemiological evaluation of treatment effectiveness (Table V). Thus, when using complex treatment in children with DU associated with *CagA (+)* strain *H.pylori*, RRR is observed 2.29 times ($\chi^2 = 6.34$, $p_{\varphi}<0.05$) with NPNT 1.59.

DISCUSSION

Successful treatment of *H pylori* infection remains a problem, especially in children [25]. Antibiotic resistance, proper adherence to treatment, and bacterial factors have been linked to the success of eradication [26]. As the prevalence of antimicrobial resistance increased, the effectiveness of the most commonly recommended treatments decreased to unacceptably low levels (≤80%), largely associated with the development of resistance to clarithromycin [27]. Children differ from adults in *H. pylori* infection in the prevalence of infection, the frequency of complications, and the higher level of antibiotic resistance [28]. In order to prevent the prevalence of resistant strains, it is very important to develop new antibacterial agents that act selectively on the unique biological characteristics of *H. pylori.* When developing new drugs against *H. pylori*, it will also be important to ensure that these agents do not affect the survival or drug resistance of other bacterial species. The hypothesis of this study was that the inclusion of VitD in the treatment of *H. pylori* infection would increase the level of eradication. This assumption was based on the fact that *H. pylori* infection leads to chronic gastritis and duodenum, ulcerogenesis and triggers immune responses [29]. VitD deficiency induces inflammatory cytokines and triggers chronic inflammation not only in the stomach but also in other organs [30]. The relationship

between *H. pylori* and serum VitD levels is currently being discussed. *H. pylori* and VitD have been suggested to be associated with gastric VitD receptors and a systemic immune response to chronic gastritis [31]. A previous study [32] showed that serum VitD levels in patients with *H. pylori*-associated gastritis lower. Several studies have examined the incidence of *H. pylori* infection in patients with varying levels of VitD [33]. Our previous study [21] showed that the effectiveness of eradication therapy for *H. pylori* infection is influenced by many factors, including the level of VitD. Children with VitD deficiency have a higher incidence of *CagA-H.pylori*. Studies have shown that vitamin D deficiency is common in patients with H. pylori and the relationship between them depends on the geographical area, which can be partly explained by the difference in exposure to ultraviolet light [34]. However, most studies that have confirmed the association of vitamin D levels in the blood with *H. pylori* were conducted without regard to geographical area.

Therefore, if VitD has a new biological effect and its levels in childhood are extremely low, and human gastric colonization of *H. pylori* is carried out in childhood, we can assume that low levels of VitD in serum correlate with the frequency of *H. pylori* infection in childhood. The aim of future research will be to elucidate the detailed antibacterial mechanism of VitD against *H. pylori* and to analyze the epidemiological relationship between its level and *H. pylori* infection in children.

Limitation. This study had some limitations. The geographical area of residence of patients, the nature of nutrition, the status of vitamin D receptors in the stomach of patients were not taken into account. Because patients with DU that were not associated with *H. pylori* were excluded from the study, it is unclear whether only patients with DU and a positive *H. pylori* test had lower VitD levels.

CONCLUSIONS

The total infection of the examined children with *H. pylori* was 90.4%. The cytotoxic strain of *CagA H. pylori* was detected in the vast majority of children examined with a positive test. The rate of H. pylori eradication in children with DU depends on the predictors of the effectiveness of AHBT - *CagA*-status and the provision of the child's body VitD. In children with H. pylori-associated DU in combination with reduced supply or deficiency of VitD, it is advisable to include in the treatment regimen an adjuvant component in the form of VitD at a dose of 2000 IU/day.

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