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ROLE OF THE SERUM VITAMIN D LEVELS AND SOME CIRCULATING MICRORNAS IN PATIENTS WITH ULCERATIVE COLITIS

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ABSTRACT

The serum levels of Vitamin D and circulating micro-RNAs (miRNAs) are subject of the current research as potential predictive and/or prognostic biomarkers in inflammatory bowel disease field. 15 miRNAs expression was assessed in 27 consecutive UC patients and then correlated with the serum level of 25(OH)D, C-reactive protein (CRP), fecal calprotectin (FCP) and Partial Mayo score. There is an inverse moderate correlation between the disease activity, measured by the partial endoscopic Mayo score and Vitamin D ($r=-0.412$; $p=0.015$). There is an inverse moderate correlation between the levels of Vitamin D and the other biochemical biomarker like FCP ($r=-0.363$; $p<0.05$). The results indicate that six miRNAs have different expression according to the serum Vitamin D levels. The expression of 4 of them: miR-28_1, miR-191_1, miR-451_1 and miR-1228-3p_1 is increased in patients with normal Vitamin D serum levels. The other two miRNAs - miR-96_1 and miR-155_2 have increased expression in Vitamin D deficiency. The results indicate that the Vitamin D deficiency carries the most significant risk for a change in the miR-1228-3p_1 serum expression level. Our results indicate that there is an inverse correlation between the serum levels of Vitamin D and some disease parameters in UC patients: FCP and the partial endoscopic Mayo score. The low Vitamin D levels also correlate with an increased miR-96_1 and miR-155_2 expression. These combined identify a promising diagnostic and treatment management approaches, using the combination of Vitamin D and miRNA levels as potential prognostic for the activity of the disease and predictive for the treatment effect biomarkers, in patients with ulcerative colitis.

KEYWORDS: Ulcerative colitis, Micro-RNA, Vitamin D, CRP & Fecal calprotectin

INTRODUCTION

Ulcerative colitis (UC) is a chronic recurrent disease of the colon with unclear etiology and pathogenesis. It is considered that genetic predisposition, microbiome changes, environmental factors and epigenetic influences are relevant in the development of UC.

There are still no reliable predictive biomarkers that could at initially at diagnosis predict the need or the type of successful treatments, as well as the potential disease evolution or treatment response. The serum levels of Vitamin D and circulating micro-RNAs (miRNAs) are subject of the current research as potential predictive and/or prognostic biomarkers.

The active form of Vitamin D, 1, 25(OH)2D3, plays an important role in the regulation of the mineral homeostasis, the wound healing and many other biological or physiological processes (1,2)

On the other hand, it has already been confirmed that 1, 25 (OH)2D3 is not only a fatty soluble vitamin, but has

immune regulatory effects over the congenital (via the dendritic cells) and the acquired (via the T lymphocytes) immune system. This influence may affect the health status or lead to the development of different diseases.

The active form of Vitamin D, 1,25$(OH)_2$D3, functions as a steroid hormone that mediates its effect via binding to the intracellular Vitamin D receptor, localized in the target cells nuclei and thus leading to the production of the active Vitamin 1,25$(OH)_2$D3 in almost all immune cells – activated CD4+, CD8+ T cells, B cells, neutrophils, antigen-presenting cells (macrophages and dendritic cells) (3).

Vitamin 1,25 $(OH)_2$D3 affects the expression of the microRNAs in the immune cells; on the other hand, the microRNAs influence over the Vitamin D signaling pathway capacity via a negative feedback (1).

It has been reported in the last years that 1,25 (OH) 2D3 (or simply referred to as Vitamin D) is implicated in many other immune mediated diseases and the expression of the microRNAs (4,5).

It induces genetic and epigenetic changes in the immune cells via influence over some miRNAs with an important regulatory function.

A recent study on human adipocytes reported that the expression of two of the most studied miRNAs in the processes of inflammation, miR-146a and miR-155, are related to the increased production of TNF-α. The addition of 1,25 $(OH)_2$D3 decreases the previously increased production of anti-TNF-α (6).

The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) signaling pathway is essential for the induction of these miRNAs. It has been suggested that the mechanism of regulation is related to the regulatory mechanism of Vitamin D to deactivate this signaling pathway. In transgenic inflammation mice models, it has been established that Vitamin D decreases the Tumor necrosis factor –alpha (TNF-α) production; this influence is also relevant not only in mice, but also in other biological subtypes (6).

miR-155 plays a key role for the immune cell functioning. It is presumed that treatment, exogenously targeting this miRNA, could lead to an improvement in a chronic inflammatory disease by counteracting and decreasing the overexpression of miR-155. This could lead to interruption of the silencing of the targeted by miR-155 genes. In other words, the exogenous treatment with 1,25 $(OH)_2$D3 could induce a change in the miR-155 expression in the immune cells.

AIM

To study the correlation between the Vitamin D levels and the expression of some miRNAs in patients with UC.

MATERIALS AND METHODS

Materials and methods: Vitamin D (25 OH D) status was measured in 23 consecutive patients with UC, who were hospitalized at the Gastroenterology clinic during a period of one year. Vitamin D serum concentrations were measured by a commercial paramagnetic particle chemiluminescent immunoassay for quantitative determination of total 25-hydroxyvitamin D [25(OH) vitamin D] levels use on Access 2 Immunoassay System. Vitamin D levels were defined as deficient if lower than 50 nmol/L; serum levels above 50 nmol/L but lower than 75 nmol/L were classified as vitamin D insufficiency.

All patients were classified according to the Montreal classification, the clinical course, the treatment regimens and the occurrence of EIMs was prospectively observed.

Disease activity was evaluated by clinical symptom, biochemical inflammatory parameters (CRP, fecal calprotectin (FCP)) and validated indices for evaluating IBD activity (Partial Mayo score). Serum levels were considered as normal if < 50mg/g for FCP and > 5mg/l for CRP.

We collected blood serum from all patients to measure the levels of miRNA, 5 ml of blood was obtained via a peripheral venopuncture with a closed system BD Vacutainer™ SST™ II Advance (Becton Dickinson, USA). Blood sample was left at room temperature for 30 minutes to coagulate. It was then centrifuged at 1500×g for 15 minutes at room temperature and the serum was separated and divided into aliquots of 500 µl and kept at −80 °C until the time of the analysis.

Isolation of miRNA was done from 200 µl serum via a commercial ready-to-use set miRNeasy Serum/Plasma Kit (50), catalogue №217184 (QIAGEN, Germany) as per protocol of the manufacturer. 3,5 µl (1,6×108 copies per µl) control miRNA C. elegans miR-39 were added to every serum sample for normalization control: miRNeasy Serum/Plasma Spike-In Control, catalogue №219610 (QIAGEN, Germany) and then the samples were eluted in 14 µl RNAse-free water.

Each of the samples was subsequently submitted to reverse transcription via ready-to-use commercial kit miScript II RT Kit (50), catalogue №218161 (QIAGEN, Germany) as per manufacturer's protocol from 2,5 µl eluted miRNA in a final volume of 10 µl with HiFlex buffer and it was incubated at 37 °C for 60 minutes and the enzyme was inactivated at 95 °C for 5 minutes.

Each of the samples was then submitted to quantitative real time polymerase chain reaction (rt-PCR) via a ready-to-use commercial kit miScript SYBR Green PCR Kit (200), catalogue № 218073 (QIAGEN, Germany) and prepared primers miScript Primer Assay (100), catalogue №218300 (QIAGEN, Germany) as per manufacturer's protocol: 1 µl complementary DNA (cDNA) in 10 µl reactions in 3-times repetitions for 15 target miRNA in 384 well plates. The used miScript Primer Assay primers(100), catalogue № 218300 (QIAGEN, Germany) are as follows (the reference number is in the brackets): Hs_miR-28_1 (MS00003255), Hs_miR-29c_1 (MS00003269), Hs_miR-96_1 (MS00003360), Hs_miR-191_1 (MS00003682), Hs_miR-451_1 (MS00004242), Hs_miR-142-5p_1 (MS00006671), Hs_miR-199a_1 (MS00006741), Hs_miR-363_1 (MS00009576), Ce_miR-39_1 (MS00019789), Hs_miR-144_4 (MS00020328), Hs_miR-142-3p_2 (MS00031451), Hs_miR-155_2 (MS00031486), Hs_miR-16_2 (MS00031493), Hs_RNU6-2_11 (MS00033740), Hs_miR-1228-3p_1 (MS00042385). The used temperature parameters are as follows: maintenance for 15 minutes at 95 °C for enzyme activation; 40 cycles of 15 seconds at 94 °C; 30 seconds at 70 °C with fluorescent reading; analysis of the melting curve in order to prove the specificity of the amplification: primary denaturation for 15 seconds at 95 °C and cooling to 55 °C for 60 seconds with an increase to 95 °C with velocity of +0,05 °C per second and fluorescent reading. The analysis was done by QuantStudio Dx instrument of Applied Biosystems (USA) company; a threshold cycle (Ct) was assessed for each sample.

The results were processed with SPSS v. 20.0 for Windows. We used variation, correlative and regression analyses as well as risk assessment analysis and comparative analyses ($\chi 2$, t-test). Significance of the obtained results was considered if $p < 0.05$ was achieved.

The clinical study was conducted after approval and permission №82 / 28.03.2019 of the Ethics commission for scientific research at the Medical University – Varna, Bulgaria.

RESULTS

Table 1 shows the characteristics of patients with UC.

Table 1: Characteristics of included Patients with UC

Index		Patients with UC (n=23)
Age, years (mean±SD, range)	Current	41.54±15.21 (18-73)
	Onset of complaints	31.28±12.05 (15-47)
	Age at diagnosis	32.74±12.77 (15-62)
Sex	Male	10/43.5 %
	Female	13/56.5 %
Localization of UC	E1	1/ 4.3 %
	E2	10/ 43.5 %
	E3	12/ 52.2 %
Course of evolution	Chronic recurrent	17/ 73.9 %
	Chronic persistent	6/ 26.1 %
Duration of CIBD, months	(mean±SD, range)	113.03±119.10 (1-492)
Treatment	5ASA	9/ 39.1 %
	Corticosteroids	7/ 30.4 %
	Immune modulators	2/ 8.7 %
	Biological treatment	5/ 21.7 %

Median Vitamin D (25(OH)D) serum expression level in patients with UC is 45.51 nmol/L ±18.57 nmol/L, with ranges from 25.66 nmol/L to 90.65 nmol/L. There is no correlation between the Vitamin D serum levels and the age of the patients. Women with UC have lower Vitamin D levels as compared to men (34.75 nmol/L ±12.98 nmol/L for females and 55.58 nmol/L ± 20.45 nmol/L for males). There is a significant difference (p=0.043) between the Vitamin D levels in patients with disease activity (40.32 nmol/L ± 15.40 nmol/L) as compared to those in remission (55.22 nmol/L ± 21.07 nmol/L). The UC activity is a risk factor for a decrease in the Vitamin D serum levels (OR=4.58 (0.733-28.646; p<0.05). The relative rate of patients with UC with Vitamin D serum levels < 50 nmol/L is 60.9 %. There is an inverse moderate correlation between the disease activity, measured by the partial endoscopic Mayo score and Vitamin D (r=-0.412; p=0.015) (Fig. 1).

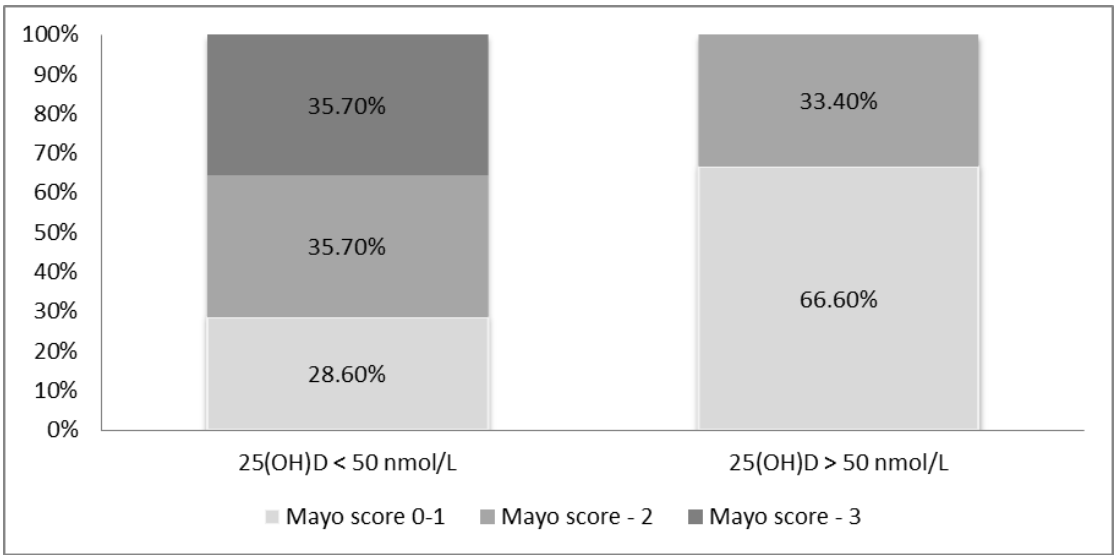

Figure 1: Correlation between Mayo score and Vitamin D Levels

There is no correlation between the levels of CRP and Vitamin D in patients with UC.

There is an inverse moderate correlation between the levels of Vitamin D and the other biochemical biomarker, FCP ($r=-0.363$; $p<0.05$) (Fig. 2).

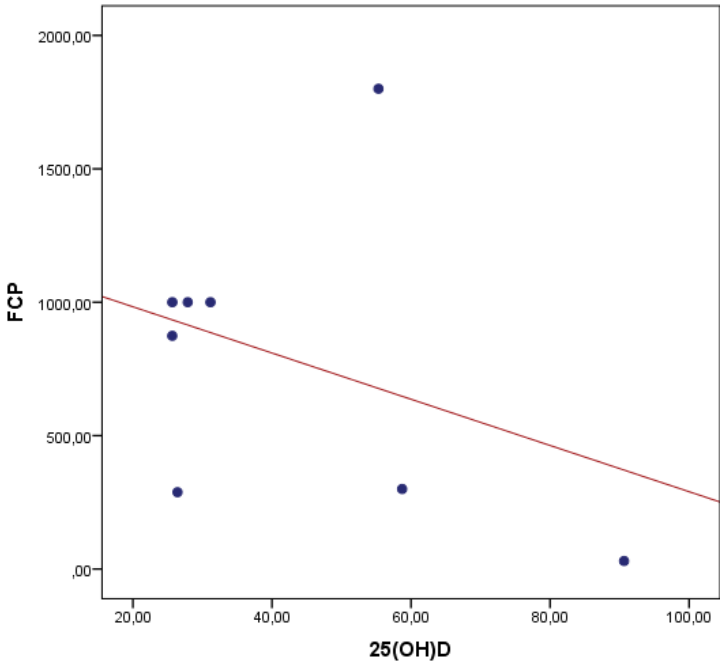

Figure 2: Correlation between the Levels of FCP and Vitamin D

Table 2 shows the expression of some miRNAs in patients with UC according to the serum Vitamin D levels. The results indicate that six miRNAs have different expression according to the serum Vitamin D levels. The expression of 4 of them: miR-28_1, miR-191_1, miR-451_1 and miR-1228-3p_1 is increased in patients with normal Vitamin D serum levels. The other two miRNAs - miR-96_1 and miR-155_2 have increased expression in Vitamin D deficiency.

Table 2: miRNAs Expression According to the Levels of Vitamin D in patients with UC

miRNA	25(OH)D < 50 nmol/L	25(OH)D ⩾ 50 nmol/L	P value	miRNA Expression Level	Vitamin D Expression Level
miR-16_2	2.32±1.24	2.34±1.73	0.571	-	-
miR-28_1	1.19±0.52	1.49±0.99	0.021	↑	↑
miR-29c_1	1.44±0.58	1.35±0.93	0.104	-	-
miR-96_1	2.22±1.89	1.66±1.31	0.050	↑	↓
miR-142-5p_1	1.66±1.02	1.37±0.88	0.966	-	-
miR-142-3p_2	1.78±0.45	1.89±1.37	0.140	-	-
miR-144_4	2.34±0.89	2.09±1.21	0.212	-	-
miR-155_2	4.34±8.58	1.45±0.95	0.025	↑	↓
miR-191_1	1.29±0.48	1.71±1.29	0.023	↑	↑
miR-199a_1	1.19±0.74	1.03±0.75	0.639	-	-
miR-363_1	2.49±1.93	2.21±1.31	0.732	-	-
miR-451_1	1.81±0.68	2.14±1.45	0.042	↑	↑
miR-1228-3p_1	1.15±0.53	1.26±0.84	0.029	↑	↑

Table 3 shows the risk analysis of the expression levels of the altered miRNAs according to the Vitamin D levels. The results indicate that the Vitamin D deficiency carries the most significant risk for a change in the miR-1228-3p_1 serum expression level.

Table 3: Risk Analysis of the expression of the miRNAs in patients with UC according to the levels of Vitamin D

miRNA	OR	95%CI	P value
miR-28_1	1.50	0.262-8.579	0.495
miR-96_1	2.00	0.352-11.364	0.036
miR-155_2	1.25	0.233-6.715	0.056
miR-191_1	1.11	0.190-6.492	0.063
miR-451_1	1.14	0.394-3.312	0.058
miR-1228-3p_1	2.18	0.713-6.678	0.015

DISCUSSIONS

Vitamin D deficiency is widely spread worldwide. Studies in healthy people in Bulgaria show a widely spread deficiency of Vitamin D (7).

Despite this, Vitamin D level measurement in clinical trials reports controversial results, most probably due to the different population included, different testing methods, trial design and Vitamin D cut-off values (8,9,10,11).

Our results show that 60.9 % of the tested patients with UC present with Vitamin D deficiency and there is a significant difference between the Vitamin D levels between patients in remission or active disease. According to some reports, the increase in the Vitamin D levels strongly correlates with a decrease in the inflammation biomarkers and the clinical activity of the disease. In an earlier report, the Vitamin D deficiency significantly correlates with increased UC activity (P = 0,04), and 68% of the patients with Vitamin D deficiency have active disease as compared to 33% of the patients with normal Vitamin D levels (12).

More recent study reports that Vitamin D levels ≤ 35 ng / mL in patients with UC in remission are related to a higher rate of further disease relapse. Patients in remission and Vitamin D levels ≤ 35 ng / mL and initial inflammation have a higher risk of earlier relapse as compared to patients with Vitamin D levels > 35 ng / mL (13). The increase of the vitamin levels may decrease the risk of relapse of the disease.

A study from Korea finds an inverse correlation between the levels of the Vitamin D and CRP in patients with Crohn's disease, whereas in patients with UC this correlation is not seen (14). Other publications as the work of Abbas et al, (15) report such inverse correlation between Vitamin D and CRP levels also in patients with UC. In a randomized placebo-controlled trial of Sharifi et al, (16) the authors report that the CRP levels are lower in patients, treated with Vitamin D as compared to those, who received placebo. The rate of patients with low FCP is significantly higher in the group of patients, treated with Vitamin D as compared to those, who received placebo. A study from Garg et al., (17) reports a significant inverse correlation between the Vitamin D levels and the FCP in patients in patients with inflammatory bowel disease (IBD). The results of our study did not establish a correlation between the serum levels of CRP and Vitamin D, similarly to the Korean study. As for the FCP, our results are in coherence with those of Garg et al., confirming an inverse correlation of the FCP with the Vitamin D levels.

To the best of our knowledge, this is the first clinical study in patients with UC, assessing the correlation between the serum concentrations of Vitamin D and expression of some circulating miRNAs.

Paraskevi et al. identify six serum miRNAs (miR-16, miR-21, miR-28-5p, miR-151-5p, miR-155 and miR-199a-5p), with increased expression in patients with UC as compared to healthy controls (18).

The current results of our study indicate a correlation of the levels of only six of all 13 studied miRNAs and Vitamin D: miR-28_1, miR-96_1 , miR-155_2, miR-191_1, miR-451_1 and miR-1228-3p_1. We are not aware of published data for a potential correlation between the expression levels of most of these miRNAs and Vitamin D in patients with UC until present. Such information is available only for the most largely studied miRNA-155.

It is established that miRNA-155 regulates the congenital immune response and the Toll-like receptors (TLR) signalization (19).The suppressor of the cytokine signalization 1 (SOCS1) is an important negative regulator, blocking the JAK / STAT signaling pathway (19,20). The rapid increase of the miR155 expression suppresses the translation of SOCS1 in inflammation and may lead to hyperinflammatory reaction. Yunzi C. et.al, (2013) (21) demonstrate that Vitamin D and the Vitamin D receptor (VDR) signaling pathway suppress the activation of NF-kB, which leads to a decrease in the miR-155 expression. The VDR pathway inhibits miR-155 via a transcriptional mechanism (22). Vitamin D blocks the induction of TNF-α, IL-6 and miR-155 in human polymorphonuclear cells in peripheral blood (PBMC) via an increase in SOCS1 regulation and suppression of the miR-155 expression. SOCS1 is a key regulator in the reverse control of the inflammation, induced by lipopolysaccharides (LPS) and this leads to a suppression of the TNF-α, IL-6 and IFN-γ signaling pathways that are essential for the chronic IBD (23). The results of our study confirm that there is a regulatory relation between the miR-155 expression and the inflammation progression in Vitamin D deficiency. We also found that the Vitamin D deficiency is responsible for the most significant risk of an increase in the miR-1228-3p_1 expression, which confirms the significance of the miR-1228/PPARs (proliferator-activated receptors) signaling pathway for the development and progression of the UC (24).

The induction of miR-1228 by Vitamin D may positively affect the osteoblasts differentiation, the mineral exchange and the bone remodulation. As in patients with chronic IBD there is a change in the bone health, related to the disease itself and/or to its treatment, the interest in this area is significant and keeps on increasing, mandating further research. As of today, there is a small number of reports on the correlation between the levels of Vitamin D and the serum miRNAs expression. This underlines the role of Vitamin D status and the expression of miRNAs on the inflammation, the metabolic processes and the development of different organs and systems (1,25).

The role of Vitamin D in patients with UC is not entirely clear yet. It is unclear whether the low Vitamin D levels lead to an increased disease activity or are a subsequent result of the severity of the UC. Our results confirm a significant inverse correlation between the levels of Vitamin D and the intestinal inflammation but which of those is the primary event, remains unclear. There is published data, from experiments in animal models, confirming the correlation between the low Vitamin D levels and the active UC (26, 27). Prospective well-designed studies are a research priority in patients with UC in order to establish the relation between the levels of FCP, the serum Vitamin D expression and some circulating miRNAs. These could be the basis of the future therapeutic management of patients with UC.

CONCLUSIONS

Our results indicate that there is an inverse correlation between the serum levels of Vitamin D and some disease parameters in patients with ulcerative colitis: the inflammatory biochemical biomarker FCP and the index for the disease activity – the partial endoscopic Mayo score. The low Vitamin D levels also correlate with an increased miR-96_1 and

miR-155_2 expression. These combined identify a promising diagnostic and treatment management approaches, using the combination of Vitamin D and miRNA levels as potential prognostic for the activity of the disease and predictive for the treatment effect biomarkers, in patients with ulcerative colitis.

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