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Plasma serotonin level in left-sided colonic diverticulosis: A pilot study

Research Article

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Abstract: Neurotransmitters might participate in the development of diverticular disease. We measured fasting and postprandial serotonin levels in colonic diverticulosis patients and healthy volunteers. We demonstrated significantly lower maximal concentrations of serotonin in patients than the controls (respectively 109.8±61.4 and 251.3±44.1 ng/ml, $p<0.001$) as well as lower serotonin minimal values (respectively 38.4±21.8 and 124.6±41.4 ng/ml, $p<0.001$) and areas under time-course curves (respectively 288.8±139.8 and 739±167.4 ng/ml, $p<0.001$); significant difference between alternating pattern and normal bowel habit concerning fasting serotonin level, the hormone response to test meal ($p=0.041$) as well as minimal serotonin level ($p=0.044$). Bowel habit was also related to peak serotonin values following a test meal with 38.5 ng/ml in constipation, 139.5 ng/ml in diarrhea, 122.4 ng/ml in alternating pattern and 249 ng/ml in subjects with normal bowel habit ($p=0.040$) as well as AUC with 120.8 ng/ml in constipation, 416 ng/ml in diarrhea, 298 ng/ml in alternating pattern and 684 ng/ml in subjects with normal bowel habit ($p=0.043$). We demonstrated substantial differences in fasting serum serotonin levels as well as the hormone response to a test meal between colonic diverticulosis patients and healthy individuals, which seemed to be associated with abnormal bowel habits rather than presence of diverticula.

Keywords: *Serotonin • Diverticulosis • Colon*

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1. Introduction

Colonic diverticulosis constitutes one of the most common abnormalities of the large bowel discovered during colonoscopy [1]. Additionally, recent studies suggest that the incidence of complications of diverticulosis is increasing now [2,3]. Recently, altered gut motility involving neurotransmitters, including serotonin, has been suggested to contribute to the development of diverticular disease in addition to other etiological factors, such as diet poor in fiber, structural abnormalities, and aging [4]. Serotonin (5-hydroksytryptamine, 5-HT) is a signaling molecule targeting enterocytes, smooth muscles and enteric neurons, the impaired signaling of which has been implicated in the pathogenesis of irritable bowel syndrome (IBS) [5]. However, studies concerning the role of serotonin in diverticular disease are limited to two conflicting papers [6,7], while the issue of blood serotonin levels has not been addressed yet. Our objective was to evaluate serotonin serum levels in a fasting and a fed state in patients with uncomplicated, symptomatic, left-sided diverticulosis as compared to healthy subjects.

2. Materials and methods

The study group consisted of patients with uncomplicated, symptomatic, left-sided colonic diverticulosis hospitalized in Department of Gastroenterology and Hepatol-

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ogy, Wroclaw Medical University (6 women, 1 man, age 45-76, mean age 65.1 years). Diagnosis of diverticulosis was made with the radiological and/or endoscopic examinations. Control group consisted of healthy volunteers recruited from hospital stuff (5 women, 2 men, age 20-35, mean age 24.7 years). Study group characteristic is presented in Table 1.

Table 1. Clinical characteristics of enrolled patients.

Patient	Sex	Age	Symptom duration	Abdominal pain	Bowel habit	Flatulence	Discomfort
1	F	75	5	+	C/D	+	+
2	M	54	4	+	C/D	+	+
3	F	76	2	+	N	+	+
4	F	68	5	+	C	-	+
5	F	68	13	+	D	+	-
6	F	45	4	+	N	+	+
7	F	70	1	+	C/D	+	+

F – females; M – males; C-constipation, D-diarrhea, N-normal bowel habit

2.1 Analytical methods

Blood was drawn by venipuncture in a fasting state and repeatedly every 30 minutes (up to 240 minutes) after a carbohydrate rich meal. Serum was obtained by blood clotting (20 minutes) and centrifugation (10 minutes; 3000/minute). Serotonin level was measured in sera with immunoenzymatical methods (ELISA) using SEROTONIN ELISA kit from DRG (Marburg, Germany).

2.2 Analytical methods

Data distribution was tested using Kolmogorov-Smirnov test and equality of variances using Levene's test. One outlying observation was detected with Tukey method in a patient's group and removed prior to correlation analysis. If not otherwise stated, data are presented as mean±SD and compared using t-test for independent samples (two-group comparisons) or 1-way ANOVA (multigroup comparisons). A repeated measure ANOVA was used to compare changes in serotonin levels in a postprandial period between patients and controls. Pearson correlation test was used for correlation analysis. Multiple regression (stepwise method) was used to identify factors independently associated with the hormone levels and to evaluate the magnitude of the association. Frequency analysis was conducted using Fisher test. All p-values were two-sided and p≤0.05 was considered significant. All the analyses were performed using MedCalc® software, version 12.0.0.0 (Mariakerke, Belgium).

3. Results

3.1 Serotonin and diverticular disease presence

Fasting serum serotonin level was significantly lower in patients than controls (Figure 1A). It corresponded with age neither in patients (r=-0.38, p=0.456) nor in controls (r=0.07, p=0.880). There was no association with disease duration (r=-0.09, p=0.867).

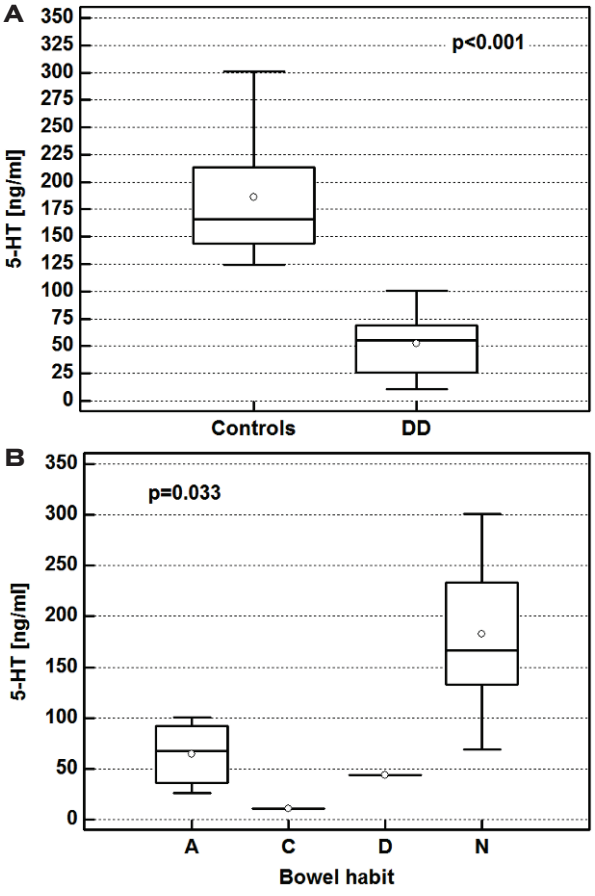

Figure 1. Fasting serum serotonin levels in study participants stratified by diverticular disease (DD) presence (A) or bowel habit (B).
Boxes represents 25 and 75 percentile; bars inside the boxes – medians; open circles – means; whiskers – 95% CI.

We also recorded changes in serotonin levels following a test meal and found significant differences between patients and controls (p<0.001) (Figure 2A). There were significantly lower peak concentrations of serotonin in patients than controls (respectively 109.8±61.4 and 251.3±44.1 ng/mL, p<0.001) as well as lower serotonin minimal values (respectively 38.4±21.8 and 124.6±41.4 ng/mL, p<0.001) and areas under time-course curves (AUCs) (respectively 288.8±139.8 and 739±167.4 ng/mL, p<0.001).

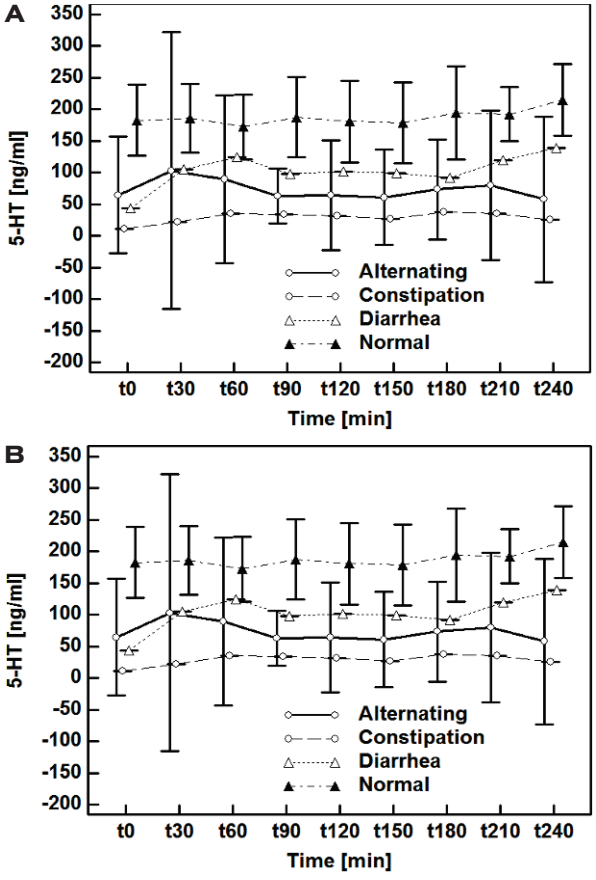

Figure 2. Mean changes in serotonin levels during postprandial time in study participants stratified by diverticular disease (DD) presence (A) or bowel habit (B).

Table 2. Correlation between fasting serotonin levels and its maximal and minimal values as well as area under time-course curves following a test meal in patients with diverticular disease (DD) and healthy controls.

Parameter	Controls	DD
Maximal value	r=0.59, p=0.163	r=0.91, p=0.013
Minimal value	r=0.09, p=0.839	r=0.94, p=0.006
Area under time-course curve (AUC)	r=0.04, p=0.937	r=0.82, p=0.048

Serotonin time-course curves in patients but not in controls seemed to be arranged in order, which was expressed by high correlation coefficients between fasting serotonin levels and peak and minimal values as well as AUCs (Table 2).

We compared time to reach a peak of serotonin in a postprandial period between patients with diverticulosis and healthy controls but found no significant differences (respectively 146±86 vs. 167±62 minutes, p=0.602).

3.2 Serotonin and bowel habit

We stratified all study participants by their bowel habit (alternating constipation and diarrhea vs. constipation vs. diarrhea vs. normal) instead of health status. There was significant difference between alternating pattern and normal bowel habit concerning fasting serotonin level (Figure 1B), the hormone response to test meal (p=0.041) (Figure 2B) as well as minimal serotonin level (respectively 40.1±25 vs. 133.1±67 ng/mL, p=0.044). Bowel habit was also related to peak serotonin value following a test meal with 38.5 ng/mL in constipation, 139.5 ng/mL in diarrhea, 122.4 ng/mL in alternating pattern and 249 ng/mL in subjects with normal bowel habit (p=0.040) as well as AUC with 120.8 ng/mL in constipation, 416 ng/mL in diarrhea, 298 ng/mL in alternating pattern and 684 ng/mL in subjects with normal bowel habit (p=0.043). Also the time to reach the peak differed between alternating pattern and normal bowel habit, being significantly shorter in the former (Figure 3).

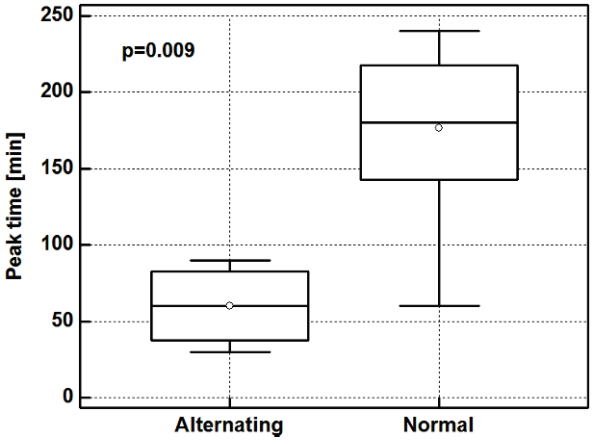

Figure 3. Time to reach a serotonin peak during postprandial period in individuals with normal and abnormal (alternating between constipation and diarrhea) bowel habit.

3.3 Multiple regression analysis

We examined which of the factors – health status (diverticulosis vs. controls) or bowel habit (abnormal (encompassing alternating pattern, constipation, and diarrhea) vs. normal) – is independently associated with serotonin blood levels. When co-examined in multiple regression analysis, bowel habit rather than diverticulosis presence was affecting the hormone levels. Bowel habit alone explained 53% variability in fasting hormone levels, 50% variability in its peak and 45% in its minimal values, and 71% in AUC.

4. Discussion

To the best of our knowledge, this is the first paper reporting alterations in blood serotonin levels in uncomplicated, symptomatic, left-sided colonic diverticulosis. We demonstrated substantial differences in fasting serum serotonin levels as well as in response to a test meal:

maximal and minimal serotonin values and areas under time-course curves following stimulation were significantly lower in diverticular disease patients.

Abnormalities in serotonin metabolism and signaling have been shown in many gastrointestinal diseases [8]. Elucidation of the role serotonin might play in colonic diverticulosis may possibly be helpful in clarification of the disease pathogenesis and in devising new treatment options. Currently, classical medical therapy recommends symptoms-targeting agents and fiber supplementation, although the role of fiber in colonic diverticulosis remains controversial [9]. Another approach encompasses antibiotics, probiotics, and anti-inflammatory agents. However, an urgent need for further studies exploring new treatment strategies including agents targeting serotonin receptors, which are already administrated in IBS is stressed [10-12].

Two available studies focused on possible involvement of serotonin in the disease development yielded conflicting results. Barenjee et al. [6] examined paired samples of the bowel, with and without diverticula, and demonstrated higher content of serotonin expressing cells as well as higher serotonin content in the latter. These authors suggested that increased hormone release may contribute to diverticulosis pathogenesis by altering colonic motility. On the contrary, Costedio et al. [7] did not find any differences in serotonin mucosal content and release between patients with diverticulosis and healthy subjects. In turn, they reported impaired reuptake of the hormone caused by decreased expression of serotonin-selective reuptake transporters (SERT) in the actively inflamed tissue from patients with diverticulitis and a similar tendency in adjacent regions. Costedio at al. concluded that abnormalities in serotonin signaling are unlikely to cause diverticula development but seem to be responsible for altered motility and symptoms accompanying diverticulosis also after recovery from acute inflammation.

Taken together, our results seem to be consistent with findings of Costedio et al. [7]. Increased serotonin release in the gut would likely be reflected by increased circulating levels of the hormone. We, however, showed decreased levels of the hormone in sera from symptomatic diverticulosis patients as compared to healthy volunteers. All differences we observed, that is, lower fasting serotonin level, lower peak and minimal values following meal, smaller AUC, and shorter time to reach the peak, occurred to be associated with abnormal bowel habit rather than presence of diverticula. Abnormal bowel habit alone explained up to 70% of variation in these measures. Hence, our observations corroborate Costedio's et al. conclusion on the relation of serotonin abnormalities with diverticulosis-associated symptoms rather than pathogenesis.

Poor platelet plasma pool of serotonin is believed to represent the amount of the hormone released by the gut. As serotonin is immediately taken up by enterocytes as well as hepatocytes from portal vein blood, only a very small portion of released hormone enters the systemic circulation, where it is scavenged and stored in platelets [13]. We measured serum level of the hormone, which represents circulating serotonin together with its platelet-stored pool. Since increased serotonin release suggested by Barenjee et al. [6] as well as its hindered reuptake suggested by Costedio et al. [7] ought rater result in increased plasma concentrations, significantly lower serotonin levels in the sera of symptomatic diverticulosis patients might imply decreased platelet pool of the hormone. Platelets, similarly to enterocytes, utilize SERT for the hormone uptake. It cannot be excluded that diverticulosis is associated with diminished SERT expression not only in the enterocytes but also in platelets.

It has been shown that postprandial serotonin release displays a pattern of sharp rises and falls [14]. Correspondingly, we found serum levels of the hormone to rise gradually neither in patients nor controls. It has also been observed that motility patterns in diverticulosis resemble these in IBS [4]. Plasma levels of serotonin in IBS patients have been reported to differ from healthy controls in a manner dependent on the disease phenotype. While IBD with predominant diarrhea has been associated with increased plasma serotonin and the number of serotonin-producing cells in gut mucosa in the background, the IBS with predominant constipation has been associated with decreased plasma hormone levels [13,14]. Although we found all diverticulosis patients with abnormal bowel habit to have attenuated postprandial serotonin serum levels as compared to healthy volunteers, a phenotype-dependent pattern found in IBS was also reflected in our patients. Limited number of observations unable us to draw final conclusions. Still, the postprandial serotonin time course curve was the lowest in constipation, middle in alternating pattern and higher in diarrhea.

An interesting observation of our preliminary study is that fasting serotonin levels seem to strongly affect its postprandial levels in diverticulosis patients, what is reflected by high correlation coefficients between fasting serotonin and its peak and minimal values as well as area under time-course curves. No such associations were found in healthy volunteers.

There was a significant age difference between patients and controls, which can be considered a limitation of present study. This, however, results from a strong dependence of colonic diverticulosis prevalence on age, which is low (~5%) in individuals below 40 but increases steeply with advancing age [4]. Nonetheless, we found no correlation between serotonin and age in both pa-

tients and controls. Limited number of observations may constitute another drawback of this study. However, number of enrolled individuals does not diverge from other preliminary studies including serial measurements of the hormone level for prolonged time (four hours in case of this study) [15]. Thus, our results can be treated as preliminary ones and their confirmation on a larger population is required.

Summarizing, we demonstrated for the first time substantial differences in fasting serum serotonin levels as well as the hormone response to a test meal between subjects with uncomplicated, symptomatic, left-sided colonic diverticulosis and healthy individuals, which seem to be associated with diverticulosis-related abnormal bowel habit rather than presence of diverticula

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