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Low Butyric Acid is Associated With Constipation in Geriatrics

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ABSTRACT

Constipation is a disorder in bowel movement indicated by reduced defecation frequency to less than three times a week. About half of worldwide geriatrics experience constipation. Short chain fatty acids (SCFAs), such as acetic, butyric, propionic and valeric acids, are the main products of microbial fermentation affecting bowel motility. Studies have shown the therapeutic effect of butyric supplements in reducing bowel pain, but less study assessed the role of SCFAs in constipation. This study evaluated levels of fecal SCFAs in 30 patients above 60 years old, both with and without constipation. No different level of SCFAs was found between constipation and non-constipation groups. Additionally, levels of acetic and propionic acids were not different between both groups. Interestingly, the level of butyric acid in the constipation group was significantly lower than the other group. The exact mechanism of how butyric acid affects constipation or constipation leads to reduced butyric acid in geriatrics remains unclear. Since butyric acid is associated with anti-inflammatory effects, increasing contractility of colonic smooth muscle and regulating intestinal neurotransmission; reduced level of butyric acid may decrease intestinal peristaltic, thus increased incidence of constipation. The future experimental study should address exact mechanism of role of butyric acids in constipation.

Keywords: Short chain fatty acids, butyric acid, constipation, geriatrics

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INTRODUCTION

Constipation is a term used to describe problems with the digestive tract movement. It is characterized by the defecation frequency of less than three times a week (1,2). Patients define constipation as difficulty in defecating, such as straining, hard stools, a feeling of incomplete bowel movements, or an unproductive urge to defecate (2). Constipation is common in older adults, where about 2.5 million people see a doctor each year. The prevalence of constipation between 22-28% and increases with age, especially those above 65 years (3,4). Constipation is chronic and difficult to treat, and it reduces the quality of life and increases economic burden (5).

Colon motility disorders, influenced by the interaction between the enteric nervous system and smooth muscle, are believed to be the main cause of constipation, however, the complete pathogenesis is not fully understood (6). The two most important constipation mechanisms in geriatrics are colon dysmotility and pelvic floor dysfunction (7,8). In recent years, the role of intestinal microecology associated with the physiological and pathological processes of the intestine has been recognized. Intestinal microbiological imbalance can cause gastrointestinal motility disorders and changes in the visceral nerves (9). Previous studies found that the number of bifid bacteria, lactobacilli, and methanogens was significantly decreased in the large intestine of constipated patients (10).

The gut microbiota and humans as hosts have a close relationship, and the interaction has positive and negative effects on human health (11). It is estimated that more than 70% of microbes are present in the large intestine (12). Besides affecting nutrition, intestinal microbes also influence through proliferation and differentiation of the epithelium, increasing the host immune system in protection against pathogenic bacteria (13). One of the main functions of bacteria found in the colon is to carry out fermentation of remaining food fibre and indigestible carbohydrates, such as pectin, gums, and cellulose (14). The main products of anaerobic microbial fermentation found in the large intestine and affecting the physiological condition of the large intestine are short chain fatty acids (SCFAs). SCFAs contain different fractions of acid, such as acetate, propionate, valeric and butyrate acids (14,15). Approximately 80-90% of SCFA resulting from food breakdown is absorbed in the intestine while the rest is excreted in the faeces (15,16). Previous studies showed that imbalance in the microbiota composition led to a significant reduction in butyrate-producing gastrointestinal microbiota (13,17) and might cause several gastrointestinal disorders, including IBS, functional constipation or colorectal carcinoma (18,19).

The nature of butyric acid and its role in the digestive tract have been known and are studied intensively. Many studies have shown that butyric acid has a role in the pathogenesis of gastrointestinal disease and has a potential therapeutic role but not fully understood. Several studies have demonstrated the potential therapeutic effects of butyrate supplements and food produced butyric acid such as butter, hard cheeses, milk, yoghurts, cream and other fermented foods (e.g. sauerkraut, pickled cucumbers, and fermented soy products, on constipation such as reducing the pain during bowel movements (20). The hypothesis is that the anti-inflammatory effect of high butyrate levels tends to limit the immune response to the gut microbiota, whereas low butyrate levels promote pro-inflammation, which impacts the remodeling state of the gut microbiota through potential pathogen suppression and recovery of butyrate-producing species (16).

As far as we notice, research on the role of butyric acid in constipation has never been carried out, especially in geriatrics, which has high constipation prevalence. Additionally, how constipation affects the level of SCFAs on feces is unknown. Therefore, this study investigated the constipation effect on the SCFA level in geriatrics.

MATERIAL AND METHODS

This cross-sectional study observed geriatrics patients with constipation (case) and without constipation (control). The study was conducted at the internal medicine ward of Dr. Zainoel Abidin Hospital Banda Aceh, Indonesia, from October 2017 to March 2018. Constipation is defined according to Rome III criteria that must include two or more of the following with insufficient criteria for diagnosis of irritable bowel syndrome: two or fewer defecations in the toilet per week, at least 1 episode of fecal incontinence per week, history of retentive posturing or excessive volitional stool retention, history of painful or hard bowel movements, presence of a large fecal mass in the rectum and history of large diameter stools that may obstruct the toilet, as previously described (21). It is caused by gastrointestinal malignancies. Patients who previously received laxative therapy, enemas, paraffin fluids, probiotics, and other laxative agents in the last three months were excluded in the study. All participants signed the informed concern after getting an explanation about the objectives of the study. Ethical clearance was approved by the Research Ethics Commission of Faculty of Medicine Universitas Syiah Kuala, Banda Aceh, Indonesia.

Fresh feces from all patients were freeze-dried, crushed and extracted according to the Folch method as previously described. The extract was then acetylated and immediately injected into Shimazhu gas chromatography (Kyoto, Japan) with a capillary column (J&W Scientific, California, USA) as the manufacturer's instruction. SCFA was calculated using the ratio of the peak area of the sample to the internal standard based on the standard curve. Percentages of fractions were also measured. All of the SCFAs measurements were conducted in Prodia, the biggest private clinical laboratory in Indonesia. Statistical analysis was performed with Graphpad® Prism® 5 (San Diego, USA). Mann-Whitney and one-way ANOVA tests were used to determine the significance of the differences in acids between two groups of constipation and non-constipation. A confident interval of 95% and a p-value <0.05 were considered significant.

RESULTS

Baseline characteristic of subjects

Thirty geriatrics patients were divided into constipation and non-constipation groups. The baseline characteristics of respondents are shown in Table 1.

More respondents with constipation were female (66.7%), while male more was more dominant in the non-constipation groups. However, both showed no statistical significance. To assess Body Mass Index (BMI) status in both groups, respondents were divided into three categories according to their BMI status: normal weight, overweight and obesity. Most patients in constipation and non-constipation groups had normal weight, 7 (43.8%) and 9 respondents (56.3%) in each group.

Fecal short chain fatty acids were not different between constipation and non-constipation

Levels of fecal SCFAs were examined and compared between the constipation and non-constipation groups. No difference in the level of SCFA was found between constipation and non-constipation groups, as shown in Figure 1.

Acetic, propionic and valeric acid were not different between constipation and non-constipation

We then continued to determine the level of SCFA fractions, both relative (percentage) and absolute, as shown in Figure 2. The percentage of SCFAs composition between constipation and non-constipation groups was significantly different, as shown in Figure 2.

There was no difference in the absolute level of acetic acid (Figure 3, left above) and propionic acid (Figure 3, right above) between the two groups. However, the absolute valeric acid (figure 3, left below), but not the relative level (figure 3, right below), was significantly lower in constipation than the non-constipation group. The valeric acid level in constipation geriatric was also relatively low compared to other acids and shared around 0-3% from the total SCFA (Figure 3, right below).

Constipation had lower fecal butyric acid levels than non-constipation geriatrics

Since the total SCFA level was not significantly different between the constipation and non-constipation groups, we then examined the butyric acid levels (both the relative and absolute levels) and compared between both groups. Interestingly, the level of butyric acid was significantly lower in the constipation than the non-constipation group, as illustrated in Figure 4.

DISCUSSION

This study assessed 30 geriatrics (15 patients each with and without constipation). The incidence of constipation in the community generally ranges from 12-19% of the total population. Constipation is more common in women (22) and this is parallel with the recent study. Additionally, the study also showed that constipation was independent of BMI status. The increase in BMI as a risk factor of constipation remains debatable since studies reported varying results. Some studies showed that constipation is related to the increased BMI. In contrast, other studies with a large population of adults showed no association between obesity and constipation (23,24). The etiology of constipation in obese patients is not well known. However, eating disorders, such as binge eating have been shown to contribute to constipation in adults (24). In addition, obese people may eat a low-fiber diet or have less daily physical activity, which can change their defecation pattern (25).

Stool samples was used to analyze micro biota of intestines due the limitation in accessibility of gastrointestinal tract. Moreover, it is also challenging since many gut micro biota cannot be cultured (26). There is a relationship between the structure of mammalian feces and micro biota (27) and SCFA act as a link between them (28). SCFAs have been shown to be important in bowel disorder, including irritable bowel syndrome (IBS) and constipation (20,28). However, we could not show the difference in the SCFA level in feces between constipation and non-constipation groups. Most patients with constipation and non-constipation had normal total SCFAs.

Although the composition of SCFAs between constipation and non-constipation groups was different, acetic and propionic acid levels were similar. The absolut level of valeric acid was lower in the constipation group but not its relative level. Since valeric acid level was very low and

share only 0-3% from the total SCFA, its role in constipation might probably not as important as butyric acid.

Butyric acid is one of SCFA's fractions that is vital in maintaining human health. It is the main source of bacterial colon energy, provides immunomodulatory effects and influences the local gene expression in many vertebrate feces (29). Approximately 70-90% of butyric acid remains in the intestine and its oxidation is higher than that of acetate and propionate. Butyrate levels are low in the systemic circulation (26,30).

Several studies have demonstrated the potential therapeutic effects of butyrate on constipation, such as reducing pain during defecation. However, the exact mechanism of how butyric acid leads to constipation is unknown. A randomized controlled study in a group of 66 patients with irritable bowel syndrome (IBS) with constipation observed a statistically significant reduction in pain during bowel movements in patients receiving sodium butyrate microencapsulation (31). Butyric acid and its salt provide anti-inflammatory effects that inhibit the production of pro-inflammatory cytokines by macrophages and monocytes, as well as reduces myeloperoxidase activity, mainly through inhibition of the activation of nuclear factor Kappa Beta (32–34).

Evidence of low-grade inflammation of the intestinal mucosa in patients with IBS and some negative changes in intestinal microflora has been reported previously (35,36) and the increased activity of myeloperoxidase in the colon was found in adult patients with IBS (37). Therefore, the reduction of intestinal inflammation can occur after butyric acid supplementation, which could potentially reduce difficulty in bowel movements, probably due to its anti-inflammation effect (20). Additionally, butyrate also supports mucosal barrier function by stimulating intestinal mucus production (38) and is able to increase peristaltic efficiency by increasing colonic smooth muscle contractility and regulating intestinal neurotransmission, especially is slow peristaltic disorder (39). In addition, all SCFAs, including butyric acid, limit the active secretion of water, sodium, and chloride ions by intestinal epithelial cells (40). All these mechanisms of action of butyric acid appear to be useful in the treatment of bowel disorders (20).

The relatively low number of participants limits the present study results, and a larger study population would provide enhanced statistical reliability. In addition, we did not consider some conditions that may lead to constipation, such as diabetes mellitus, drugs, and other geriatrics related psychological conditions. Another limitation is the fact that we could not eliminate the environmental factors, such as diet and other factors related to microbiota.

CONCLUSION

The study showed that lower levels of fecal butyric acid are associated with the increased incidence of constipation in geriatrics probably because butyric acid mediates anti-inflammatory effects, increasing the contractility of colonic smooth muscle and regulation of intestinal neurotransmission. Therefore, the reduced level of butyric acid may decrease the intestinal peristaltic, thus increased the incidence of constipation. Future experimental studies should address the exact mechanism of butyric acids' role in constipation.

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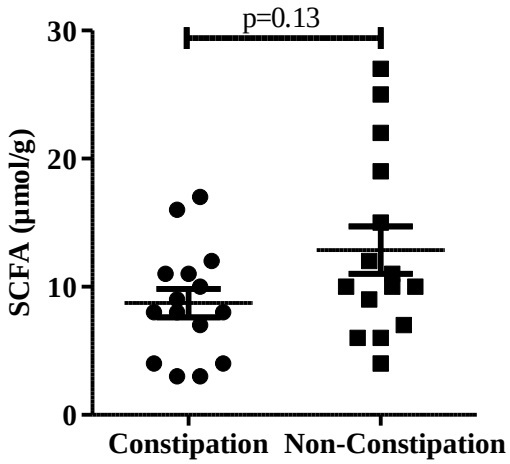
"Table 1: Baseline characteristic of respondents according constipation status."

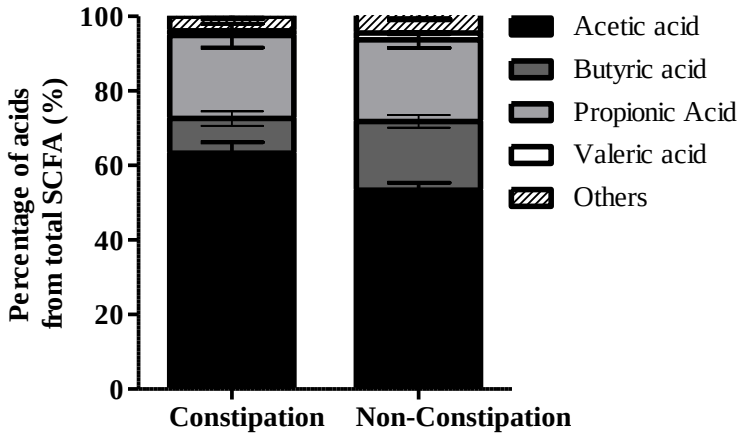
Variables	Constipation status n (%)		p-value
	Yes	No	
Sex			0.068[a]
Males	5 (33.3)	10 (66.7)	
Females	10 (66.7)	5 (33.3)	
Body Mass Index			0.797[b]
Normoweight	7 (43.8)	9 (56.3)	
Overweight	4 (57.1)	3 (42.9)	
Obesity	4 (57.1)	3 (42.9)	

[a] *Chi-square tests*
[b] *Fisher's exact test*

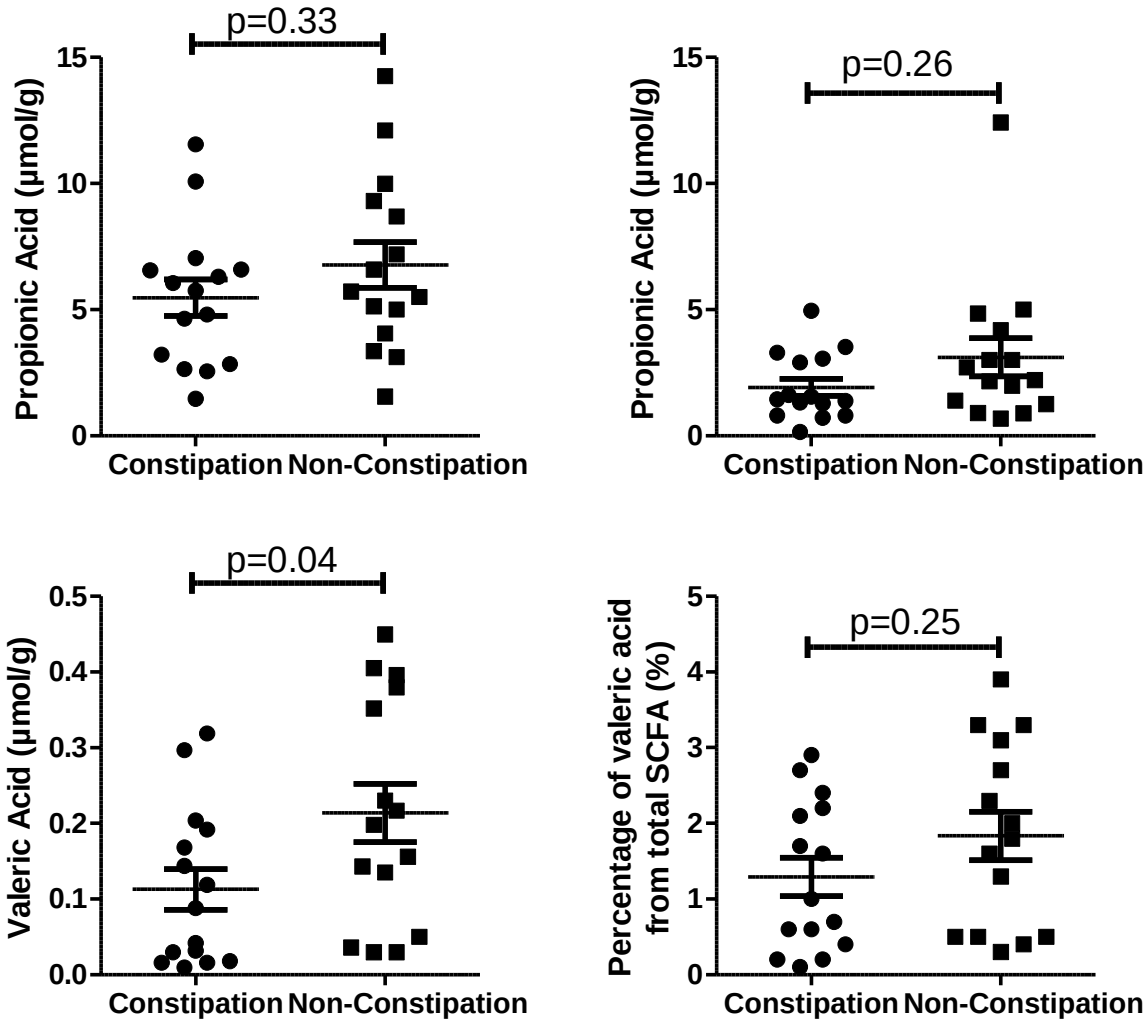
"Figure 1: Fecal Short chain fatty acids level between constipation and non-constipation groups"



"Figure 2: Level of SCFAs' fractions of acetic, propionic and valeric acids in both groups"



"Figure 3: Level of acetic (left above), propionic (right above) and valeric acids both absolute (left below) and relative (right below) between constipation and non-constipation groups."



"Figure 4: Relative (left) and absolute (right) levels of fecal butyric acid in constipation and non-constipation geriatrics."