Short Chain Fatty Acids Level are Associated with Lipid Profile in Patients with Coronary Slow Flow

Original Research Article

ABSTRACT

Background: The phenomenon of Coronary Slow Flow (CSF) is an angiographic clinical verity, which is characterized by late opacification of the distal segments of the coronary artery without having significant stenosis. However, a definite and reliable mechanism of CSF is still not known. Short-chain fatty acids (SCFA) such as acetate, butyrate, and propionate are produced as a result of the fermentation of indigestible dietary fibers in the gut by the microbiota. Many studies have investigated the role of SCFA as a related signaling pathway in inflammation, glucose metabolism, and lipid metabolism. In this study, we investigated the correlation between Short Chain Fatty Acids and Lipid Profile serum in Patients with Slow Flow Coroner.

Materials and Methods: A cross sectional study was conducted at dr. Zainoel Abidin Hospital of Banda Aceh. All consecutive patients scheduled for coronary angiography between July 2021 to Desember 2021. CSF was diagnosed based on the Thrombolysis In Myocardial Infarction (TIMI) frame count (TFC) of coronary flow. Data was obtained through laboratory examination and stool samples. Stool samples were analyzed for SCFA (acetate, propionate, and butyrate acids) with gas chromatography.

Results: The results of the present study indicate that SCFA, acetate, propionate, and valerate did not show a significant correlation with lipid profile (P>0.05). The level of fecal butyrate was negatively correlated with HDL (p=<0.05; r = -0.532).

Conclusions: Our study indicated that the level of butyrate was a moderate negative correlated with HDL inpatient with slow flow coroner.

Keywords: SCFA; lipid profile; coronary slow flow.

1. INTRODUCTION

"The phenomenon of Coronary Slow Flow (CSF) is an angiographic clinical verity, which is characterized by late opacification of the distal segments of the coronary artery without having a significant stenosis" (1). Small vessel, diffuse atherosclerosis, vascular inflammation, endothelial dysfunction, and platelet aggregation dysfunctions are some of the theories that have been proposed to explain the pathophysiology of CSF (2,3). "The gut microbiota has been demonstrated to have a key role in the progression of atherosclerosis, but the exact mechanism remains unknown. Short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate, are metabolites created by bacterial fermentation in the colon from otherwise indigestible polysaccharides (fibres)" (4). In rodents and humans, SCFAs have been found to reduce plasma concentrations of cholesterol. Propionate is being considered as a possible contender for decreasing plasma cholesterol levels; however, the outcomes of trials evaluating are controversial (5,6).

2. MATERIALS AND METHODS

2.1 Patients and Study Design

This is a cross-sectional study that included fifty patients from July 2021 to Desember 2021 in the Division of Cardiology, Internal Medicine Department, Faculty of Medicine, University of Syiah Kuala, Banda Aceh and Cardiac Catheterization Laboratory at dr. Zainoel Abidin Hospital of Banda Aceh. Exertional chest pain suggestive of stable angina pectoris or positive or inconclusive results of non-invasive screening

tests for myocardial ischemia had all led to referral to coronary angiography. Among them, the patients who had no coronary plaque disease and having delayed coronary flow rate were selected for the study. Individuals who had active antibiotic treatment or within the month prior to angiography, yogurt consumption or laxative medicine for the last four weeks or who had undergone surgery for intestinal tumors were excluded from the study. "All angiographic examinations were conducted by two cardiologist who were blinded to the clinical characteristics of the patients assessed the flow in coronary arteries using the Thrombolysis in the Myocardial Infarction (TIMI) frame count method, described" by Gibson et al (7). The whole blood were analyzed for fasting blood sugar (FBS), total cholesterol (TC), triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C).

2.2 Gas Chromatography Analysis of Faecal SCFA Concentration

Stool samples were analysed for SCFA concentration with gas chromatography (GC) as described from a previous method (8). The amounts of acetate, propionate, butyrate and valerate acids have been reported as mg/ml and %.

2.3 Statistical Analysis

The results of the statistical analysis were presented as mean standard deviation or median (interquartile range) for normally and non-normally distributed continuous variables, and number (percentages) for nominal variables, respectively. The Shapiro-Wilk test was employed to determine whether the variable distributions were normal. The intensity and correlation between the two quantitative variables were investigated using the Pearson correlation test (in the case of a normal distribution) and Spearman's correlation test (in the event of a non-normal distribution). All of the tests were carried out at a 0.05 significance level.

3. RESULTS

A total of 50 patients joined in the study. Table 1 demonstrated the characteristics of the patients. Of these, 24 (48%) were male and the mean age of the studied population was 44.9 years old. The mean of fecal concentrations of acetate, propionate, butyrate, valerate, absolute butyrate and total SCFA were 58.13 %, propionate is 21.67 %, valerate is 2.34%, absolute butyrate is 2.34 mg/ml, and total SCFAs is 15.40 mg/dl, respectively.

Table 2 presents the association between short-chain fatty acids (SCFAs) with Lipid Profile. TC, LDL and TG not significantly correlated with SCFA but Pearson's correlation revealed a significant inverse correlation between HDL and butyrate acids ($r = -0.532$; $p=<0.05$) (Fig. 1).

Table 1. Characteristics of Subjects

Variable	CSF (n=50)
Age (years)	44.93 ± 11.13
Sex, male female	24 (48%)/26 (52%)
BMI (kg/m^2)	23,24±2,86
SBP (mmHg)	140 (109 – 191)
DBP (mmHg)	86 (63 – 148)
Hemoglobin (g/dl)	14.30 (10.5 – 16.6)
WBC (ul)	9900±2600
Platelet (10^3/ul)	301 (150 – 406)
Neutrophil-lymphocyte count ratio	1.78 (0.81 – 7.3)
Total Cholesterol (mg/dl)	164 (117 – 297)
LDL cholesterol (mg/dl)	107.27 ± 27.79
HDL cholesterol (mg/dl)	47 (16 – 77)
Triglyceride (mg/dl)	91 (72 – 269)
Urea (mg/dl)	26.20 ± 10.4
Creatinin (mg/dl)	1 (0.5 – 1.20)
Random blood glucose (mg/dl)	93.60 ± 17.43
Short Chain Fatty Acids (SCFA)	
Acetate Acids (%)	58.13 ± 7.29

Propionate Acids (%)	21.67 ± 6.58
Butyrate Acids (%)	12.2 ± 3.7
Valerate Acids (%)	2.34 ± 0.98
Absolute Butyrate Acids (mg/dl)	2.34 ± 1.26
Total SCFAs (mg/dl)	15.40 ± 5.6
TIMI Frame Count	
LAD (frame)	53,07±10,35
LCX (frame)	50,20±9,6
RCA (frame)	60,73±12,30

Data were presented as mean±SD, median (minimum-maximum) or n (%). BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; ESR: Erythrocyte Sedimentation Rate; LDL: Low-density Lipoprotein; HDL, High-density Lipoprotein. RCA: Right Coronary Artery; LCx: Left Circumflex Artery; LAD: Left Anterior Descending Artery; TIMI: Thrombolysis in Myocardial Infarction Frame Count

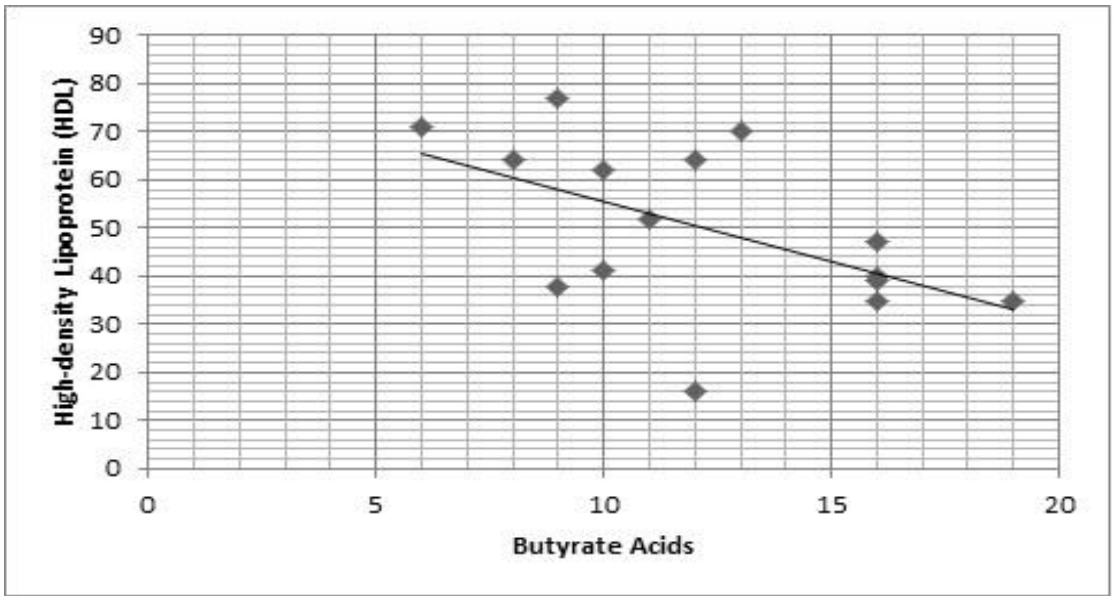

Fig. 1. A negative correlation between butyrate acids with High-density Lipoprotein (HDL)

Table 2. The associations between short-chain fatty acids (SCFAs) with Lipid Profile

	TC	**LDL**	**HDL**	**TG**
	r (*P* value)	**r (*P* value)**	**r (*P* value)**	**r (*P* value)**
Acetate Acids	0.063(0.823)	0.168(0.55)	0.325(0.237)	0.331(0.228)
Propionate Acids	0.081(0.773)	-0.327(0.234)	0.003(0.992)	-0.472(0.076)
Butyrate Acids	-0,230 (0.410)	-0.188(0.503)	-0.532(0.041)*	-0.033(0.907)
Valerate Acids	-0.135(0.631)	-0.026(0.926)	-0.275(0.321)	0.409(0.130)
Absolute Butyrate Acids	-0.280(0.312)	-0.437(0.103)	-0.1(0.722)	-0.394(0.146)
Total SCFAs	-0.108(0.701)	-0.354(0.196)	0.379(0.163)	-0.506(0.055)

**: p value correlation is significant at 0.05 level, r: Pearson's correlation coefficient*

4. DISCUSSION

The gut microbiome is a growing topic of research in metabolic health and its link to CVD risk (9). "SCFAs are produced by the microbiota through the fermentation of ingestible polysaccharides and proteins, and are thought to represent the link between the microorganisms and the host. Individual SCFAs have also been shown to play a role in metabolism; for example, acetic acid supplementation reduces weight gain and improves glucose tolerance in obese people and diabetic rats" (10), "butyric acid protects against obesity and increases thermogenesis in mice" (11), and "propionic and butyric acids improve glucose homeostasis in mice" (12). **"**By interacting with the diet, changes in the gut microbiota disrupt not only metabolism but also the composition of the host's lipids" (13). Dyslipidaemia has changed with SCFA,

especially HDL. According to our findings, HDL is negatively correlated with butyrate acid in a patient with slow flow coroner.

“Gut dysbiosis is generally characterized by a decrease in microbial population diversity and stability, and blooms in certain harmful bacteria” (14). “Insulin resistance and abnormal level of short chain fatty acids (SCFAs) can occur from the metabolic network within the host harboring dysbiotic microorganisms being altered in situ” (11). The phylum Firmicutes produces butyric acid, the phylum Bacteroidetes produces propionic acid, and the majority of anaerobic bacteria make acetate (15).

Short-chain fatty acids appear to play a role in the regulation of fatty acid, glucose, and cholesterol metabolism in cells. SCFAs have the ability to control lipolysis and adipogenesis. Endogenous lipolysis is inhibited by acetate and propionate, whilst extracellular lipolysis is regulated by propionate via a rise in lipoprotein lipase production, resulting in a decrease of the circulating lipid plasma levels and body weight (16,17). In rat colonic epithelial cells that convert SCFAs to acetyl-CoA, Zambell et al. discovered that acetate and butyrate are the predominant synthetic lipid substrates (18). “Finally, acetate, propionate, and butyrate appear to promote hepatic cholesterol uptake from the circulation, decreasing plasma cholesterol in model animal experiments. Furthermore, propionate inhibits cholesterol production effectively” (19).

According to Granado-Serrano et al., participants with hypercholesterolemia had higher abundances of Odoribacter (Bacteroidetes) and Ruminococcus (Firmicutes) and lower abundances of Anaeroplasma (Tenericutes) and Haemophilus influenzae (Proteobacteria) (20). Fu et al. found a negative connection between TG levels and the Pasteurellaceae genus (21). Anaeroplasma abundance was also linked to an unfavorable lipid profile (IDL-C, TG-related biomarkers and the ratio Total-C to HDL-C among others) (20). The level of acetic acid in the feces was linked to IDL-C levels, which are linked to a more unfavorable lipid profile, but not propionic acid. Although there were no significant differences in serum levels of acetic and propionic acids between groups, hypercholesterolemia showed a profile with higher and lower abundance of acetic and propionic acids, respectively, than normocholesterolemia. “These findings are in line with prior research that found that circulating acetic acid stimulated "de novo" lipogenesis and cholesterogenesis in the liver, while propionic acid inhibited it” (20-23). There was no significant link between the lipid profile and the examined SCFA, acetate, propionate, and valerate in our study.

A study by *Granado*-Serrano *et al reported that* “there was no difference in the abundance of butyrate in feces between hypercholesterolemia and normocholesterolemia,and there was no association with any of the lipid biomarkers studied. However, in normocholesterolemia, its serum levels were greater, indicating a negative relationship with lipids associated with a worst profile, such as LDL-C, Total-C, LDL-TG, LDL-P (large and small), and Total-C to HDL-C ratio among others” (20). Butyrate has been shown to promote fatty acid production and cholesterogenesis in prior study (19). On the other hand, a study published by Gao Z et al. found that adding butyrate supplementation to the diet can help prevent other metabolic diseases including insulin resistance in rats, and this is linked to an energy expenditure and mitochondrial function activation pathway (11). Butyrate levels were shown to be inversely linked with HDL in our study ($p=0.05$; $r = -0.532$).

This study had some limitations that should be considered when interpreting the results. First, with a larger research population and a lower number of participants, statistical reliability would be improved. Secondly, this study was performed only in participants with slow flow because the limited numbers participants with normal coroner. Third, no samples of the gut microbiota were collected for this study, therefore the idea that particular bacteria influence lipid and liver profile indicators through the generation of SCFAs could not be directly evaluated. However, no other investigations on SCFA and lipid profile in patients with CSF have lately been undertaken or published.

5. CONCLUSION

In conclusion, the finding of this study show that dyslipidemia, especially HDL level, is associated to butyrate acids in patients with slow flow coroners. Other parts of this association appear to require more research.

CONSENT

As per international standard or university standard, Participants’ written consenthas been collected and preserved by the author (s).

ETHICAL APPROVAL

The study was approved by the Ethical Review Committee of Medical Faculty, Syiah Kuala University, Banda Aceh, Indonesia

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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