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High salt intake enhances hepatic lipid accumulation via modulation of gut microbiota

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ABSTRACT: Long-term excessive salt intake is a risk factor for hypertension, but its impact on lipid metabolism and gut microbiota remains poorly understood. This study aims to evaluate the effects of inadequate or excessive salt intake on lipid metabolism and gut microbiota composition, and explore the underlying relationship between these effects. Male Syrian golden hamsters were randomly assigned to six groups and fed diets with sodium chloride levels of 0.4, 0.8, 3.0 (a normal dose), 6.0, 12.0 or 24.0 g/kg for nine weeks. Lipid levels in plasma, liver and feces were measured, and fresh feces were analyzed via 16s rRNA gene sequencing. Results showed that neither inadequate nor excessive salt intake altered plasma lipids. However, excessive salt intake led to a dose-dependent increase in liver lipid accumulation. Additionally, it significantly modified gut microbiota composition at the family and genus levels. Notably, higher salt doses reduced both the relative abundance of *Allobaculum* and fecal short-chain fatty acids (SCFA) concentrations, with a positive correlation being observed between the two. These findings suggest that excessive salt intake aggravates hepatic lipid accumulation, likely by modulating gut microbiota involved in SCFA production.

Keywords: salt; sodium chloride; lipid metabolism; short-chain fatty acids; gut microbiota; *Allobaculum*

1. Introduction

Sodium is a key electrolyte indispensable for maintaining life activities. As one of the major salts in the body, it plays a critical role in maintaining fluid balance, supporting neuromuscular function, and facilitating nutrient absorption. The World Health Organization (WHO) recommends that the daily salt intake of adults be limited to less than 5 grams. While the minimum sodium requirement to meet human physiological needs remains undefined, sodium deficiency is rare in healthy populations due to the widespread presence of salt in both natural and processed foods. In contrast, excessive salt consumption is a severe health issue globally. Both animal studies and population studies have demonstrated that long-term excess salt intake is a major cause of hypertension [1-3].

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Beyond its role in hypertension, excessive salt intake may also influence other cardiovascular risk factors, such as hyperlipidemia (dyslipidemia). Research indicates that high salt consumption not only elevates blood pressure but it may also disrupt lipid metabolism [4]. For instance, an early study in rabbits fed a high-cholesterol diet showed that adding 1% salt in diet significantly raised plasma triacylglycerol levels and worsened coronary atherosclerosis [5]. Similarly, in rats, an 8% high-salt diet led to an marked increases in plasma total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG), alongside a notable decrease in high-density lipoprotein cholesterol (HDL-C) [6]. Population studies echo these findings, linking high sodium intake to dyslipidemia and insulin resistance. Furthermore, epidemiological data suggest a positive correlation between sodium consumption and the incidence of non-alcoholic fatty liver disease (NAFLD) [7, 8]. Collectively, these results indicate that excessive salt intake may heighten the risk of cardiovascular and metabolic diseases by promoting lipid accumulation.

However, the relationship between salt intake and lipid metabolism is not entirely straightforward, as some studies suggest that insufficient salt intake may also disrupt lipid profiles. In Wistar rats, strict salt restriction increased plasma triglycerides and cholesterol by 71% and 10%, respectively [9]. A systematic review of 167 studies comparing low- versus high-sodium diets found that low-sodium groups exhibited significantly higher plasma cholesterol and triglyceride levels [10]. In $LDLR^{-/-}$ mice, a low-salt diet (0.15% sodium chloride or 0.01% sodium) was shown to promote lipid deposition in the aortic wall and accelerate atherosclerotic lesion development [11, 12]. Human trials have yielded similar results: healthy male subjects on a 3-week sodium-restricted diet (20 mmol/day) experienced significant increases in plasma TC and LDL-C levels [13]. Additionally, a survey of overweight hypertensive women revealed a negative correlation between sodium intake and blood cholesterol levels [14]. These findings suggest that inadequate salt intake may impair normal lipid metabolism, potentially leading to elevated blood lipid levels.

To date, research has primarily focused on two areas: (i) the impact of high salt intake on hypertension, and (ii) the effects of high or low salt intake on blood lipid profiles in mice or rats. The gut microbiota, increasingly recognized as a critical link between diet and host health, has not been adequately explored in this context. Notably, no studies have investigated how varying salt intake levels—whether excessive or insufficient—affect hepatic lipid concentrations and gut microbiota composition, nor have they examined potential connections between these outcomes. To address this gap, the present study examines the effects of salt doses ranging from 0.4 to 2.4 g/kg on plasma and liver lipid concentrations, as well as gut microbiota composition. Hamsters were selected as the model organism due to their suitability for studying cholesterol metabolism.

2. Materials and methods

2.1. Materials

An AIN-93M-MX mineral mix without sodium chloride was obtained from Ready Biotechnology (Shenzhen) Co., Ltd. Sodium chloride (> 99.5%) was obtained from Scharlab, S. L. (Barcelona, Spain). Casein and vitamin mix were obtained from Harlan Teklad (Madison, WI, U.S.A.). D, L-methionine and

cholesterol were provided by Sigma-Aldrich (St. Louis, MO, U.S.A.). Corn starch, sucrose, lard and gelatin were purchased from a local market.

2.2. Preparation of diets

Typically, 3g/kg sodium chloride is a normal dietary concentration of salt [15]. Six semi-purified diets with different concentrations of sodium chloride were prepared according to the AIN-93 diet by mixing the following ingredients: 242 g casein, 504 g corn starch, 119 g sucrose, 50 g lard, 40 g mineral mix, 20 g vitamin mix, 20 g gelatin, 1 g DL-methionine, 1 g cholesterol and sodium chloride (group 1: 0.4 g/kg diet, 1/8X; group 2: 0.8 g/kg diet, 1/4X; group 3: 3.0 g/kg diet, 1X; group 4: 6.0 g/kg diet, , 2X; group 5: 12.0 g/kg diet, 4X; group 6: 24 g/kg diet, 8X).

2.3. Animals, group and feeding

Sixty healthy male Syrian golden hamsters (*Mesocricetus auratus*), weighing 100–120 g, were sourced from the Laboratory Animal Services Centre at the Chinese University of Hong Kong. Following a one-week acclimation, they were randomly assigned to six groups (n=10 each) and fed diets with sodium chloride at 0.4, 0.8, 3.0, 6.0, 12, or 24 g/kg—corresponding to 1/8, 1/4, 1, 2, 4, and 8 times the normal intake—for nine weeks. Housed individually at (25 ± 1)℃ with a 12-hour light/dark cycle, the hamsters had free access to food and water, with weekly recordings of food intake, water consumption, and body weight. Fecal samples were collected at week 9 and stored at -20℃, with fresh feces gathered over the last three days of week 9. After overnight fasting at week 9, blood was sampled from the retro-orbital sinus under isoflurane anesthesia into heparinized tubes. At the end of the experiment, hamsters were euthanized under carbon dioxide anesthesia, and liver, heart, kidney, testis, perirenal fat, and epididymal fat were harvested, weighed, and stored at -80℃. All procedures were approved by the Animal Experimentation Ethics Committee of the Chinese University of Hong Kong (Ref No. 21-169-MIS).

2.4. Plasma lipid analyses

Plasma samples were obtained by centrifugation at 3000r/min. Plasma concentrations of TC, TG and high density lipoprotein cholesterol (HDL-C) were measured with specific commercial kits (Stanbio Laboratories, Boerne, TX, U.S.A.). Plasma non-HDL-C concentrations were calculated by subtracting HDL-C concentrations from TC concentrations.

2.5. Measurement of hepatic cholesterol

Liver cholesterol was measured as previously described [16, 17]. Briefly, 0.1 g liver tissue was mixed with 1.0 mg 5α-cholestane (internal standard) in a 50 mL Falcon tube, homogenized in 18 mL chloroform/methanol/saline (10:5:3, v/v/v) using a Polytron homogenizer, and centrifuged at 3000 r/min. The lower layer was saponified, converted to trimethylsilyl (TMS) ether derivatives, and analyzed on a Shimadzu GC-2010 with a Supelco SAC™-5 column (30 m x 0.25 mm x 0.25 μm) and flame ionization detector.

2.6. Measurement of hepatic and fecal lipids

Hepatic and fecal lipids were measured in quantity of fatty acids including saturated fatty acids (SFA), monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) as previously described [18, 19]. Briefly, 0.3 g of liver tissue or feces was combined with 0.6 mg heptadecanoic acid (internal standard) in a 50 mL falcon tube, homogenized with 18 mL chloroform/methanol/saline (10:5:3, v/v/v) using a Polytron homogenizer, and centrifuged at 3000 r/min for 10 min. The lower layer containing hepatic or fecal lipids was dried under nitrogen, treated with 14% boron trifluoride methanol to form methyl esters, and analyzed on a Shimadzu GC-2010 gas chromatograph with an HP-Innowax column (30 m x 0.32 mm x 0.5 μm) and flame ionization detector.

2.7. Measurement of neutral and acidic sterols in the feces

Fecal neutral and acidic sterols were quantified per Hao et al [20]. About 300 mg of feces was mixed with 0.5 mg 5α-cholestane and 0.6 mg hyodeoxycholic acid as internal standards. The mixture was saponified with 1N NaOH at 90℃ for 1 h, extracted with cyclohexane, and the upper layer was converted to TMS derivatives for neutral sterol analysis. The aqueous layer was saponified with 10N NaOH at 120℃ for 4 h, extracted with diethyl ether, and processed into TMS derivatives for acidic sterol analysis. Both were analyzed using a Shimadzu GC-2010 instrument.

2.8. Fecal short chain fatty acid analyses

Fecal short chain fatty acids (SCFAs) were measure per Hao et al [21]. Approximately 300 mg of feces was combined with 0.1 mg 2-ethylbutyric acid (internal standard), extracted ultrasonically with 5 mL acidic 50% ethanol for 20 min, and centrifuged at 12,000 g for two 10-min cycles. The supernatant was analyzed on a Shimadzu GC-2010 system with a CP-FFAP CB capillary column (25 m x 0.32 mm x 0.30 μm).

2.9. 16S ribosomal RNA (rRNA) gene sequencing and analyses

Fresh feces were collected from each cage (five cages per group, n=5) over the final three days of the experiment, freeze-dried, and analyzed via 16S rRNA gene sequencing per Liu et al [17].and He et al [22]. Microbial DNA was extracted using the E.Z.N.A. Fecal DNA Kit (Omega Bio-tek, Norcross, GA, USA) and amplified targeting the V3-4 region of the 16S rRNA gene with primers 338F (5'-ACTCCTACGGGAGGCAGCAG-3') and 806R (5'-GGACTACHVGGGTWTCTAAT-3') on an ABI GeneAmp® 9700 thermocycler (ABI, CA, USA). Sequencing was conducted on an Illumina MiSeq PE300 platform (Illumina, San Diego, USA) with the MiSeq Reagent Kit v3. Sequences were quality-checked with Trimmomatic, merged with FLASH, and clustered into operational taxonomic units (OTUs) at > 97% similarity using Usearch (v7.0). After leveling, community abundance at phylum, family and genus levels was determined using R software, with additional analyses performed as per Liu et al [17] and Hao et al [20].

2.10. Statistical analyses

Data were presented as means ± standard deviations (SD). Group differences were assessed using SPSS 16.0 via one-way analysis of variance (ANOVA) with a *post-hoc* LSD test. Spearman's correlation and linear

regression analysis were used to evaluate correlations. Significant differences ($P < 0.05$) between groups were denoted by distinct lowercase letters.

3. Results

3.1. Body weight, food intake, water consumption and relative organ weights

Table 1 presents the average body weight, food consumption, water intake, and relative organ weights of hamsters across groups. Feeding salt (sodium chloride) at doses of (0.4–24) g/kg for 9 weeks did not alter average body weight. Daily water intake rose with increasing sodium chloride doses, while no notable differences were observed in daily food intake or relative organ weights across groups.

Table 1 Body weight, food intake, water intake and feces output in hamsters fed the diets supplemented with different level of sodium chloride.

Salt (g/kg diet)	0.4	0.8	3.0	6.0	12.0	24.0	*P* value
Food intake (g/d)	9.7 ± 1.0	9.2 ± 0.6	9.9 ± 0.4	9.7 ± 1.5	9.4 ± 0.7	9.6 ± 0.7	0.85
Water intake (g/d)	7.0 ± 1.8b	7.5 ± 1.6b	7.6 ± 1.3b	11.3 ± 2.4a	11.6 ± 2.1a	12.0 ± 2.9a	< 0.01
Feces (g/d hamster)	0.35 ± 0.06	0.33 ± 0.05	0.34 ± 0.03	0.36 ± 0.06	0.33 ± 0.02	0.35 ± 0.03	0.86
Body weight (g)	128.1 ± 9.0	125.4 ± 6.4	132.1 ± 12.6	134.4 ± 18.1	129.3 ± 12.3	127.6 ± 8.4	0.58
Relative organ weight, % of body weight							
Liver	5.27 ± 0.53	5.16 ± 0.41	5.29 ± 0.48	5.13 ± 0.32	5.24 ± 0.32	5.11 ± 0.56	0.91
Kidney	0.88 ± 0.07	0.87 ± 0.08	0.86 ± 0.08	0.87 ± 0.07	0.89 ± 0.05	0.94 ± 0.04	0.13
Testis	1.51 ± 0.71	1.65 ± 0.76	1.99 ± 0.58	1.94 ± 0.59	2.21 ± 0.51	1.90 ± 0.86	0.26
Heart	0.41 ± 0.03	0.41 ± 0.03	0.41 ± 0.03	0.41 ± 0.04	0.41 ± 0.02	0.41 ± 0.03	0.99
Perirenal fat	1.13 ± 0.21	1.20 ± 0.19	1.31 ± 0.20	1.24 ± 0.15	1.26 ± 0.18	1.24 ± 0.25	0.43
Epididymal fat	1.37 ± 0.26	1.46 ± 0.34	1.49 ± 0.32	1.50 ± 0.26	1.59 ± 0.25	1.49 ± 0.31	0.69

All data were presented as mean ± SD. One-way ANOVA was used to compare the differences among different groups by a *post-hoc* LSD test. Different superscript letters [a, b] represented significant difference as $P < 0.05$.

3.2. Plasma fasting glucose, TC, TG, HDL-C, non-HDL-C and non-HDL-C/TC

Plasma concentrations of fasting glucose, TC, TG, HDL-C, non-HDL-C and non-HDL-C/TC ratio at week 0 and 9 are presented in Table 2. A salt intake of 0.4 g/kg to 24 g/kg did not lead to significant variations in the concentration of plasma fasting glucose, TC, TG, HDL-C, non-HDL-C and non-HDL-C/TC of hamsters in any groups.

Table 2. Plasma lipids in hamsters fed the diets supplemented with different level of sodium chloride at Weeks 0 and Week 9.

Salt(g/kg diet)	0.4	0.8	3.0	6.0	12.0	24.0	*P* value
Week 0							
TC (mg/dL)	134.93 ± 11.79	136.48 ± 12.60	136.04 ± 20.45	134.95 ± 12.10	139.02 ± 17.09	136.17 ± 17.82	0.99
TG (mg/dL)	63.40 ± 10.82	63.70 ± 8.96	66.42 ± 7.12	62.40 ± 17.68	62.56 ± 17.40	59.63 ± 7.35	0.9
HDL-C (mg/dL)	120.71 ± 6.86	118.37 ± 6.55	119.92 ± 8.89	117.83 ± 14.45	119.26 ± 8.71	119.92 ± 6.33	0.98
non-HDLC (mg/dL)	14.23 ± 10.09	18.11 ± 11.99	16.14 ± 16.55	17.11 ± 9.40	19.79 ± 17.30	16.26 ± 14.78	0.97
non-HDLC/TC	0.10 ± 0.07	0.13 ± 0.09	0.11 ± 0.10	0.13 ± 0.08	0.13 ± 0.11	0.11 ± 0.09	0.96
non-HDLC/HDLC	0.12 ± 0.09	0.15 ± 0.10	0.13 ± 0.13	0.15 ± 0.1	0.17 ± 0.16	0.13 ± 0.12	0.94
Week 9							
Fasting glucose	4.51 ± 0.61	4.18 ± 0.69	4.08 ± 0.51	4.18 ± 0.43	3.98 ± 0.59	4.26 ± 0.77	0.50
TC (mg/dL)	232.2 ± 30.6	239.1 ± 28.8	238.7 ± 35.9	241.9 ± 24.4	241.8 ± 21.7	238.1 ± 34.1	0.98
TG (mg/dL)	124.7 ± 25.8	136.8 ± 18.0	136.8 ± 38.4	141.6 ± 51.3	155.2 ± 43.3	149.3 ± 69.6	0.71

HDL-C (mg/dL)	126.5 ± 13.7	127.6 ± 10.7	126.3 ± 8.8	125.9 ± 10.2	125.8 ± 9.0	128.8 ± 11.0	0.98
non-HDLC (mg/dL)	105.7 ± 27.9	111.5 ± 22.0	112.4 ± 36.9	115.9 ± 21.2	116.0 ± 19.8	109.3 ± 24.9	0.94
non-HDLC/TC	0.45 ± 0.07	0.46 ± 0.04	0.46 ± 0.08	0.48 ± 0.05	0.48 ± 0.05	0.45 ± 0.04	0.85
non-HDLC/HDLC	0.85 ± 0.26	0.87 ± 0.15	0.90 ± 0.33	0.92 ± 0.18	0.93 ± 0.17	0.84 ± 0.14	0.91
Body weight (g)	128.1 ± 9.0	125.4 ± 6.4	132.1 ± 12.6	134.4 ± 18.1	129.3 ± 12.3	127.6 ± 8.4	0.58
Food intake (g/d)	9.7 ± 1.0	9.2 ± 0.6	9.9 ± 0.4	9.7 ± 1.5	9.4 ± 0.7	9.6 ± 0.7	0.85
Water intake (g/d)	7.0 ± 1.8b	7.5 ± 1.6b	7.6 ± 1.3b	11.3 ± 2.4a	11.6 ± 2.1a	12.0 ± 2.9a	< 0.01
Feces (g/d hamster)	0.35 ± 0.06	0.33 ± 0.05	0.34 ± 0.03	0.36 ± 0.06	0.33 ± 0.02	0.35 ± 0.03	0.86

All data were presented as mean ± SD. Different superscript letters [a, b] represented significant difference as $P < 0.05$.

3.3. Liver cholesterol and lipids

The effects of different level of dietary salt on hepatic lipids, including cholesterol and fatty acids, were analyzed. Compared to normal dietary salt (3g/kg) group, low-salt diet (0.4, 0.8 g/kg) showed no significant effects on hepatic cholesterol or fatty acid content in hamsters. In contrast, a high-salt diet (24 g/kg) significantly elevated hepatic cholesterol, monounsaturated fatty acids (MUFA), and total fatty acid levels by 27.7%, 25.4% and 17.6%, respectively (Fig. 1A-E). Further, correlation analysis showed that dietary salt intake was positively correlated with liver cholesterol, MUFA, total fatty acids levels in hamsters (Fig. 1F-H). Taken together, those findings indicated that excessive intake of dietary salt could lead to the accumulation of lipids in the liver.

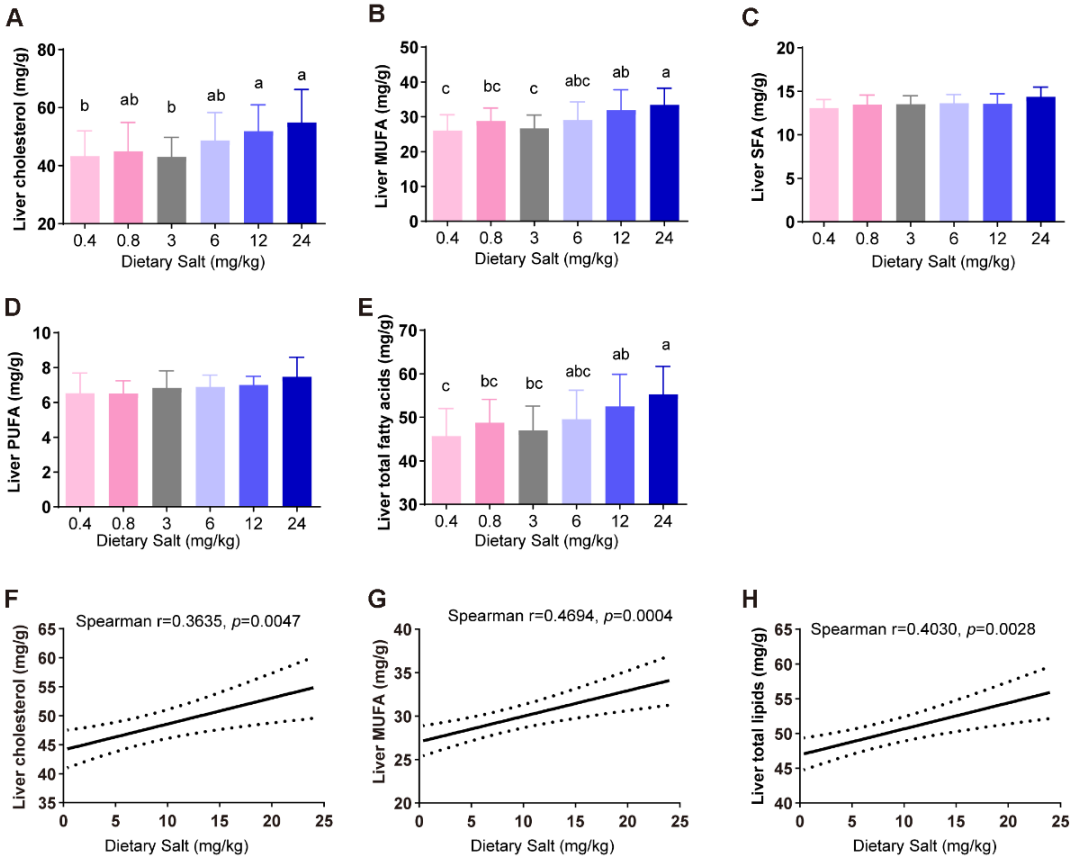
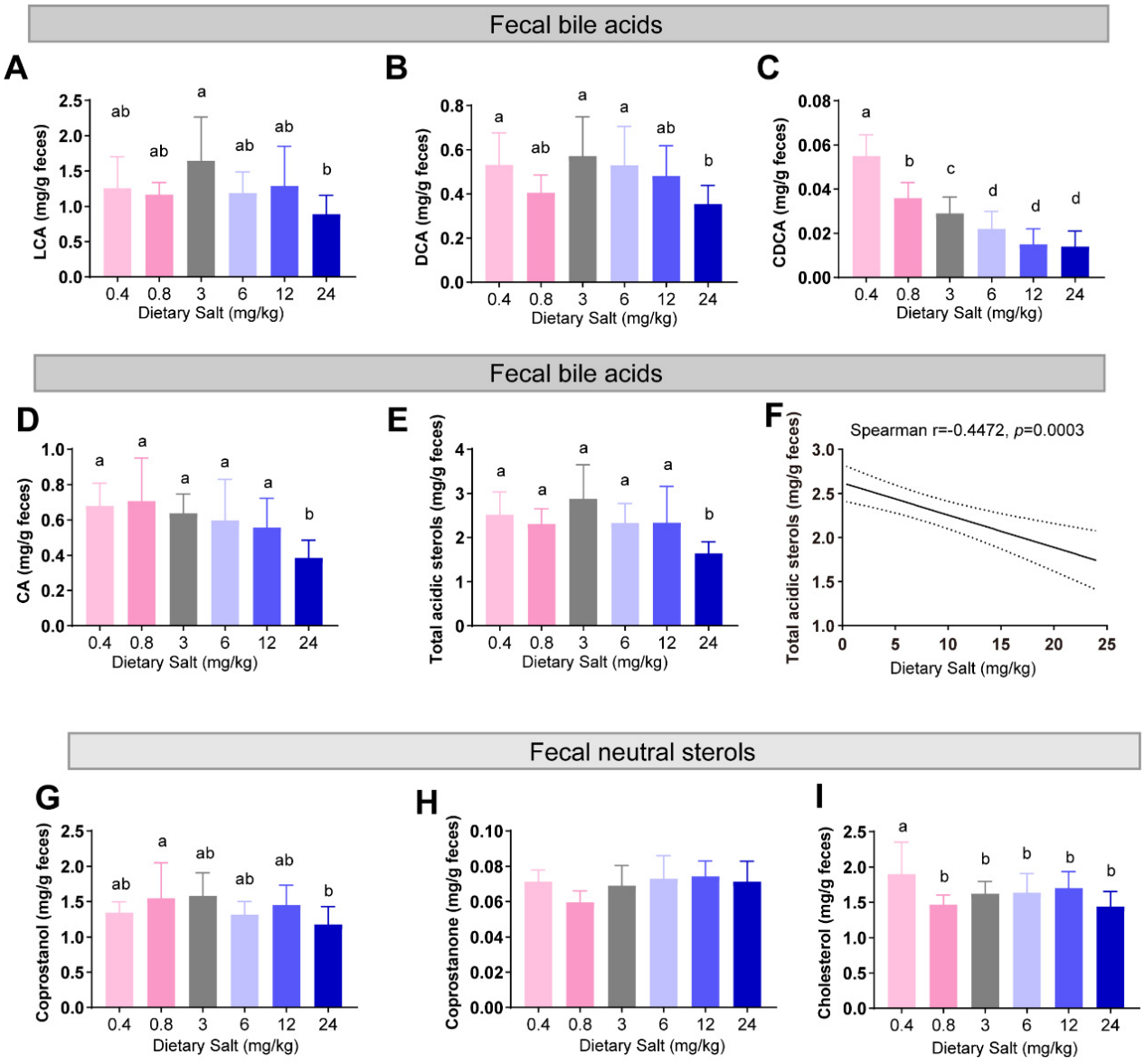


Figure 1. The levels of liver lipids profile in hamsters fed the diets supplemented with different level salt. (A) Liver cholesterol. (B-E) Liver monounsaturated fatty acids (MUFA), saturated fatty acids (SFA), polyunsaturated fatty acids (PUFA) and total fatty acids. (F-G) Significant correlation between dietary salt and liver cholesterol, MUFA and total fatty acids. All data were presented as mean ± SD. Different superscript letters [a, b, c] represented significant difference as $P < 0.05$.

3.4. Fecal neutral acidic sterols and fatty acids,

Hepatic lipids homeostasis is closely linked to intestinal dietary absorption and hepatic elimination via bile acid excretion. Fecal neutral, acidic sterols and fatty acids were then analyzed. When compared to the normal-salt diet (3g/kg) group, low-salt diet (0.4/0.8 g/kg) had no effect on fecal acids sterols, except for an increasing in chendeoxycholic acid (CDCA) level. In contrast, high-salt supplementation (24 g/kg) markedly reduced the excretion of lithocholic acid (LCA), deoxycholic acid (DCA), CDCA, and cholic acid (CA) (Fig. 2A-D), thereby decreasing total fecal acids sterols in a dose-dependent manner (Fig. 2E-F). Similarly, the low-salt diet had no significant effect on fecal neutral sterol excretion (Fig. 2G-K). However, high-salt administration (24 g/kg) could significantly decrease the fecal dihydrocholesterol and total neutral sterols by 26.3% and 19.2%, respectively (Fig. 2G, I). Further correlation analysis revealed a significant negative association between dietary salt intake and fecal total neutral sterols in hamsters (Fig. 2L). Additionally, fecal fatty acids level was comparable among different salt supplementation groups (Table 3). Collectively, these findings demonstrate that excessive dietary salt intake enhances intestinal absorption of neutral sterols while suppressing bile acid excretion.



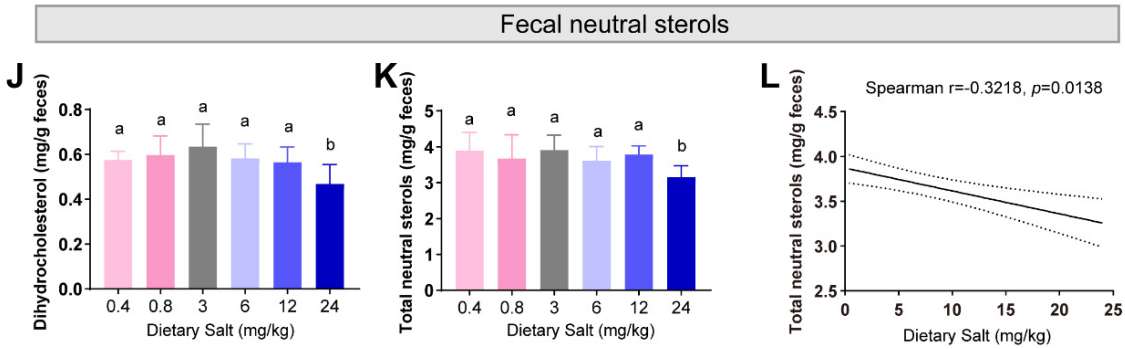


Figure 2. Fecal acidic and neutral sterols profiles in hamsters fed the diets supplemented with different level of salt. (A-E) The levels of fecal lithocholic acid (LCA), deoxycholic acid (DCA), chendeoxycholic acid (CDCA), cholic acid (CA) and total acidic sterols. (F) Correlation between dietary salt and total acidic sterols level. (G-K) The levels of fecal coprostanol, coprostanone, cholesterol, dihydrocholesterol and total neutral sterols. (L) Correlation between dietary salt and total neutral sterols levels. All data were presented as mean ± SD. Different superscript letters [a, b, c] represented significant difference as $P < 0.05$.

Table 3. The levels of fecal fatty acids in hamsters fed the diets supplemented with different level of salt.

Salt (g/kg diet)	0.4	0.8	3.0	6.0	12.0	24.0	*P* value
Fecal fatty acids (mg/g feces)							
SFA	15.74 ± 3.39	16.37 ± 1.09	15.23 ± 2.26	14.81 ± 2.42	14.51 ± 2.01	15.39 ± 0.66	0.79
MUFA	3.86 ± 0.65	3.79 ± 0.36	3.55 ± 0.64	3.48 ± 0.47	3.56 ± 0.51	3.92 ± 0.35	0.65
PUFA	0.44 ± 0.08	0.44 ± 0.05	0.40 ± 0.05	0.39 ± 0.06	0.39 ± 0.04	0.43 ± 0.04	0.49
Total fatty acids	20.70 ± 4.08	21.26 ± 1.25	19.83 ± 2.85	19.38 ± 2.85	19.09 ± 2.53	20.36 ± 0.97	0.78
Fecal fatty acids, % of total fatty acids							
SFA	76.84 ± 1.57	78.52 ± 2.22	77.77 ± 1.58	77.28 ± 1.53	77.22 ± 1.62	76.50 ± 1.47	0.90
MUFA	19.36 ± 1.43	17.71 ± 2.23	18.41 ± 1.57	18.93 ± 1.24	19.02 ± 1.65	19.76 ± 1.35	0.43
PUFA	3.80 ± 0.17	3.77 ± 0.21	3.81 ± 0.39	3.79 ± 0.31	3.76 ± 0.09	3.74 ± 0.15	0.99

SFA: saturated fatty acids; MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids. All data were presented as mean ± SD. Different superscript letters [a, b, c, d] represented significant difference as $P < 0.05$.

3.5. Fecal SCFA level

Fecal SCFAs mainly comprise acetic, propionic, butyric and valeric acid. As shown in Figure 3, neither low- nor high-salt diets significantly altered fecal propionate or butyrate levels compared with the normal-salt diet (3 g/kg), although a modest reduction in valeric acid was observed in the 0.8 g/kg group (Fig. 3B, C, D). Notably, an obvious decreasing trend in acetic acid and total SCFAs production was observed across salt supplementation groups (0.4-24 g/kg) (Fig. 3A, E), a significant trend further confirmed by correlation analysis (Fig. 3F, G). Taken together, those results showed that dietary salt intake could decrease the fecal acetic acid and total SCFAs production in a dose-dependent manner.

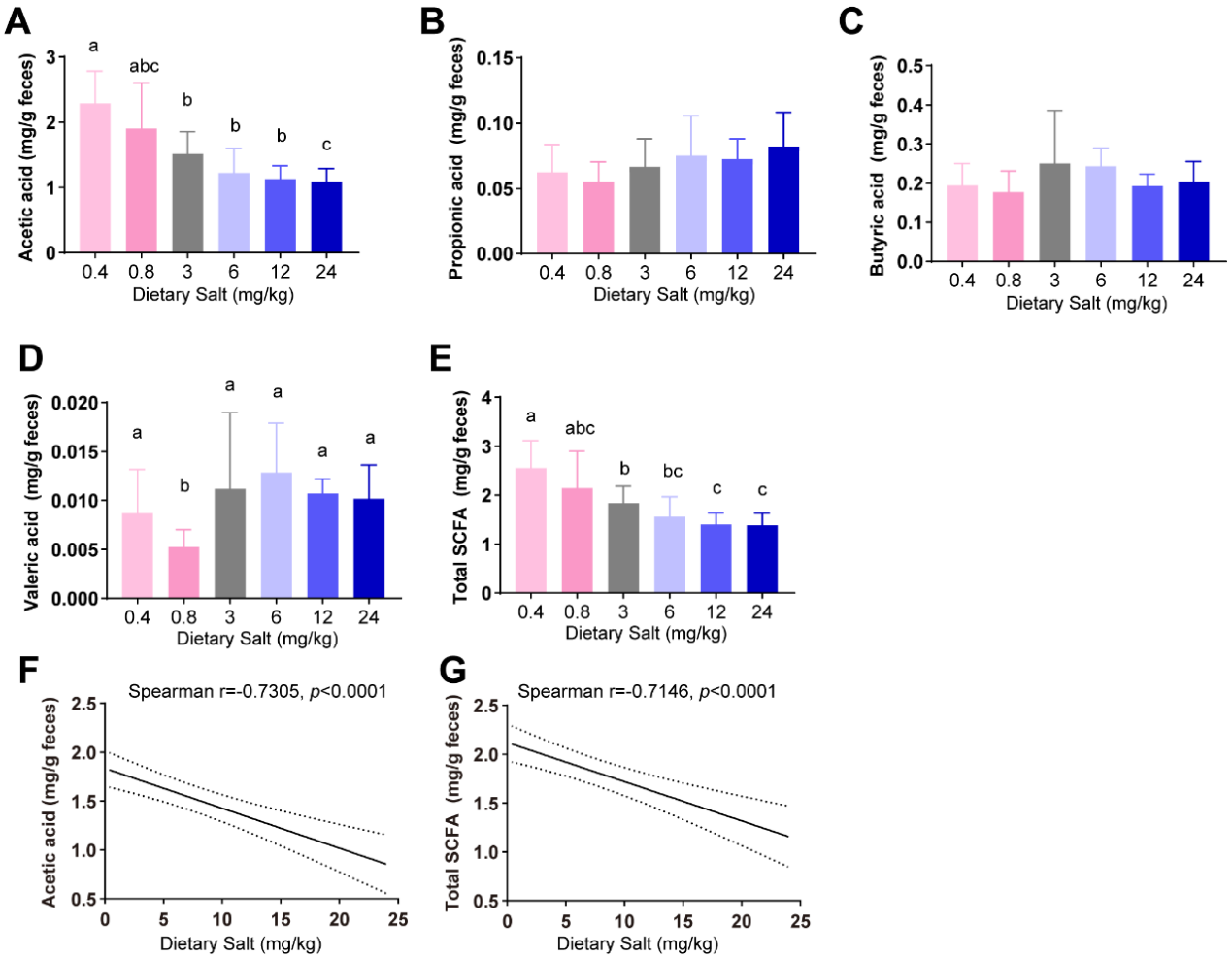


Figure 3. Fecal SCFA profile in hamsters fed the diets supplemented with different level of salt. (A-E) The levels of fecal acetic acid, propionic acid, butyric acid, valeric acid and total SCFAs. (F, G) Correlation between dietary salt and fecal acetic acid and total SCFAs levels. All data were presented as mean ± SD. Different superscript letters [a, b, c] represented significant difference as $P < 0.05$.

3.6. Gut microbial diversity and composition

To study the impact of varying salt intake on gut microbes, 16S rRNA sequencing were performed. From 2,755,316 raw reads, 1,414,991 valid sequences were obtained and clustered into 431 OTUs at 97% similarity (data not shown). Alpha diversity, assessed via Chao and Shannon indexes, showed that 24.0 g/kg salt intake resulted in the lowest microbial richness and diversity, though differences across doses were not significant (Fig. 4A, B). Beta diversity, evaluated through PCoA, revealed distinct microbial profiles between the normal (3 g/kg) and highest (24.0 g/kg) salt doses (Fig. 4C). Venn diagrams indicated all groups shared 313 OTUs, with the 24.0 g/kg dose linked to the lowest OTU abundance (Fig. 4D). Those results suggest that while dietary salt intake (both low and high) may not significantly alter gut microbiota diversity, it could modulate microbial community composition.

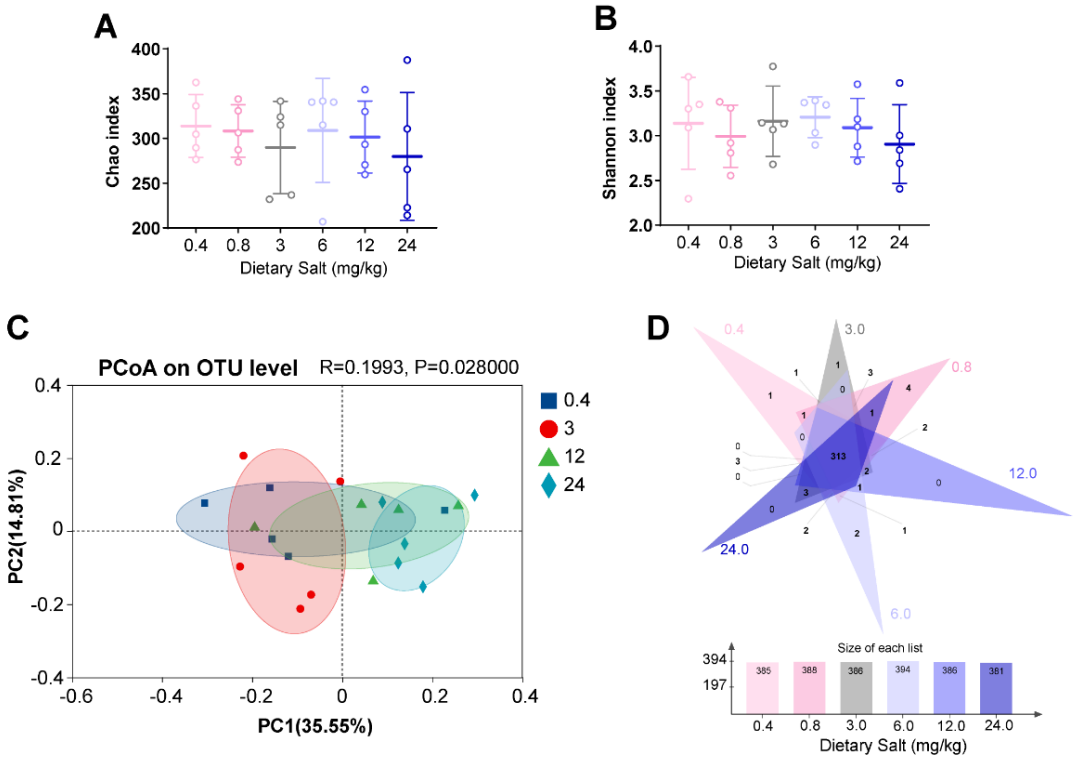


Figure 4. Gut microbiota diversity in hamsters fed the diets supplemented with different level of salt. (A, B) Chao index and Shannon index as the estimators of the community richness and diversity of gut microbiota. (C) Principal coordinate analysis (PCoA) plot at the operational taxonomic unit (OUT) level. (D) Venne diagram showing the unique and shared OTUs of gut microbiota.

Hence, the impact of varying dietary salt levels on gut microbiota composition was assessed at phylum, family, and genus levels (Fig. 5A-C). At the phylum level, *Firmicutes* and *Bacteroidetes* predominated, with their relative abundances unaffected by varying salt intake (Fig. 5D, E). At the family level, *Bacteroidales_S24-7_group*, *Erysipelotrichaceae*, *Ruminococcaceae*, *Eubacteriaceae*, *Lachnospiraceae*, *Bacteroidaceae*, *Prevotellaceae*, *Alcaligenaceae* and *norank_o_Gastranaerophilales* were found to be dominant in all six groups of hamsters (Fig. 5B). Salt intake significantly changed the relative abundance of *Erysipelotrichaceae* (decreased from 0.4 to 24 g/kg), *Ruminococcaceae* (increased from 6-24 g/kg)and *Helicobacteraceae* (increased from 0.8-24 g/kg) in a dose-dependent way (Fig. 5F, G, H). At the genus level, thirteen genera, comprising *norank_f_Bacteroidales_S24-7_group*, *Allobaculum*, *norank_f_Eubacteriaceae*, *norank_f_Ruminococcaceae*, *Bacteroides*, *Coprococcus_2*, *unclassified_f_Lachnospiraceae*, *norank_o_Gastranaerophilales*, *Parasutterella*, *Prevotellaceae_UCG-003*, *Lachnospiraceae_NK4A136_group*, *[Eubacterium]_coprostanoligenes_group* and *Prevotellaceae_Ga6A1_group*, were prevalent (Fig. 5C). Compared with the normal-salt diet group (3 g/kg), the relative abundance of *Allobaculum* showed a significant dose-dependent decrease, whereas *norank_f_Ruminococcaceae* and *Helicobacter* exhibited a corresponding dose-dependent increase (Fig. 5I-N).

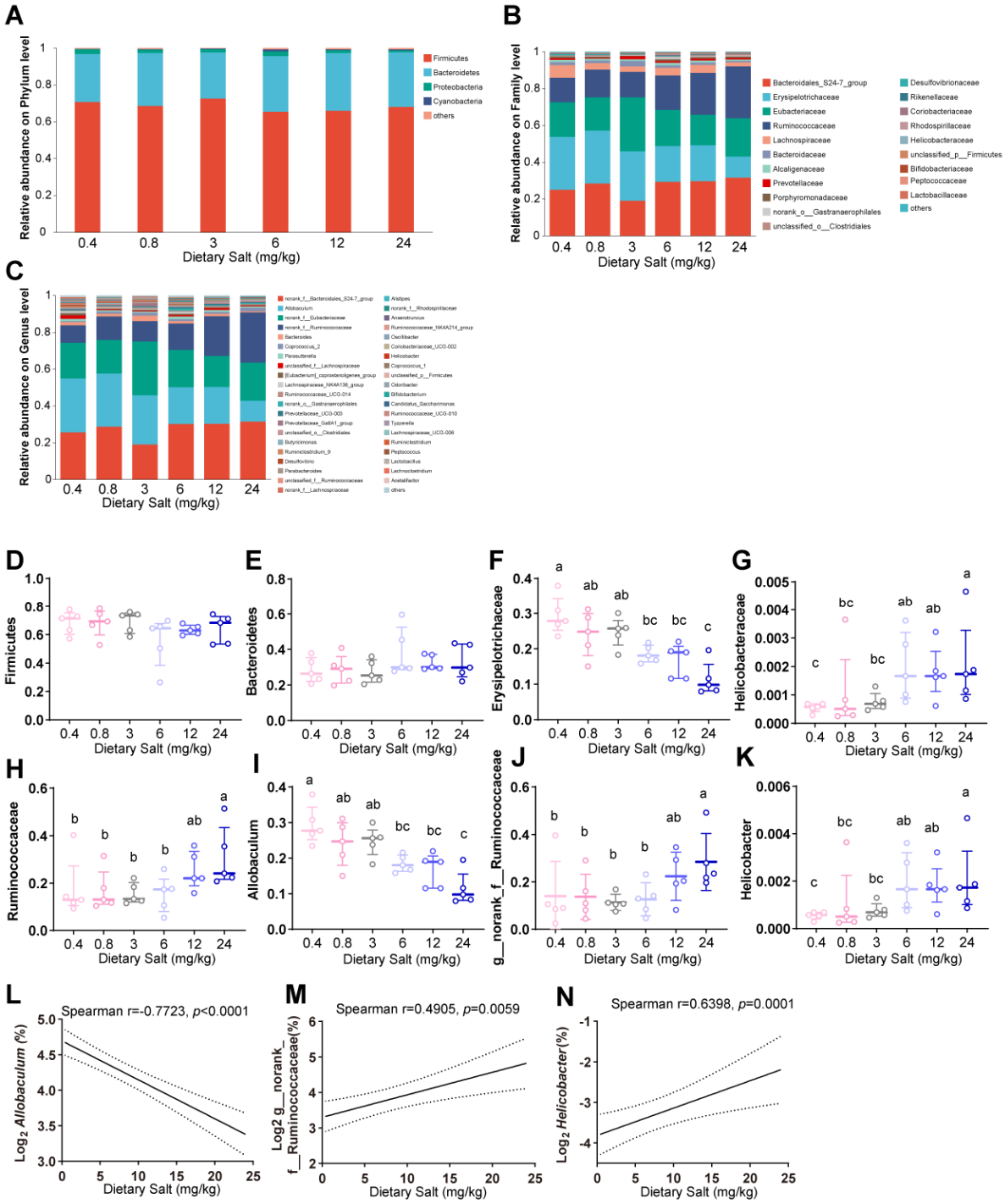


Figure 5. Gut microbiota composition in hamsters fed the diets supplemented with different level of salt. (A-C) Community abundance at the phylum level, family level and genus level. (D-E) Relative abundance of *Firmicutes* and *Bacteroidetes* at the phylum level. (F-H) Relative abundance of *Erysipelotrichaceae*, *Ruminococcaceae* and *Helicobacteraceae* at the family level. (I-K) Relative abundance of *Allobaculum*, *norank_f_Ruminococcaceae* and *Helicobacter* at the genus level. (L-N) Correlation between dietary salt and Log$_2$ *Allobaculum*(%), Log$_2$*norank_f_Ruminococcaceae*(%), and Log$_2$ *Helicobacter* (%) levels. Different superscript letters $^{a, b, c}$ represented significant difference as $P < 0.05$.

3.7. Correlation of specific microbiota at the genus level with lipid metabolism parameters

Spearman's correlation analyses explored the relationship between the top 50 gut microbial genera and lipid parameters, including liver cholesterol, fecal neutral and acidic sterols, and liver and fecal fatty acids (Fig. 6). Thirty-one genera correlated with at least one lipid metabolism parameter, with positive associations in red and negative in green. In particular, *Allobaculum* positively correlated with fecal neutral sterols,

individual (deoxycholic acid, chenodeoxycholic acid, cholic acid) or total acidic sterols, total SCFAs and the major SCFA (acetic acid), and inversely with liver cholesterol, individual and total fatty acids. *Bacteroides* showed positive links to fecal neutral (e.g., coprostanol, dihydrocholesterol), total and individual acidic sterols, and negative links to liver cholesterol and fatty acids. *Bifidobacterium* positively associated with fecal MUFAs, PUFAs, and total fatty acids, and negatively with fecal coprostanol, dihydrocholesterol, lithocholic acid and total acidic sterols. *Helicobacter* positively correlated with liver cholesterol and negatively with fecal dihydrocholesterol, lithocholic acid, chenodeoxycholic acid and total acidic sterols. *Prevotellaceae_Ga6A1_group* positively linked to fecal neutral sterols and deoxycholic acid and valeric acid, and negatively to liver MUFAs. *Unclassified_o_Clostridiales* positively associated with liver fatty acids and negatively with fecal cholesterol, chenodeoxycholic acid and acetic acid. *Unclassified_p_Firmicutes* positively correlated with fecal coprostanol, cholesterol and total neutral sterols, and negatively with liver MUFAs.

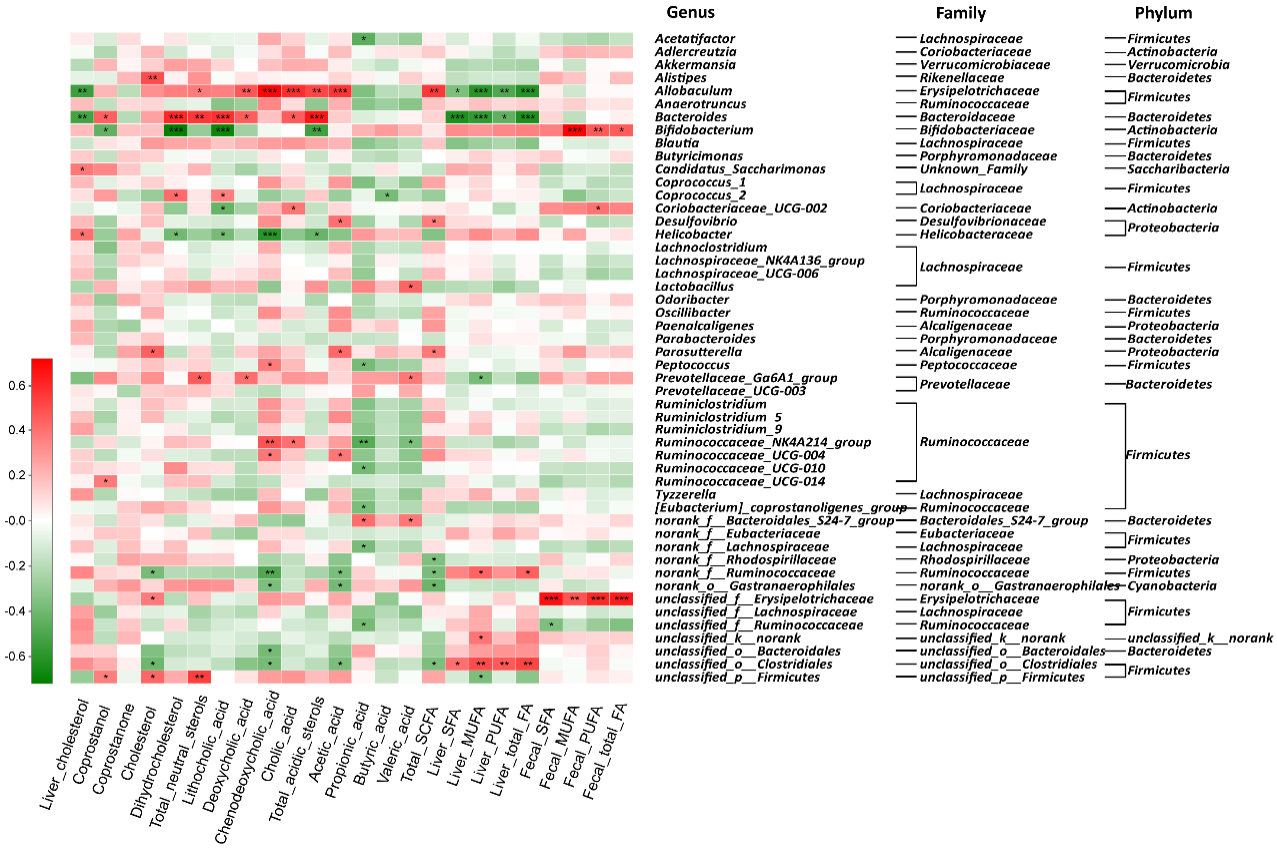


Figure 6. Spearman's correlation analyses between top 50 genera and those lipid-related parameters including liver lipids, fecal lipids and fecal SCFAs in hamsters fed the diets supplemented with different level of sodium chloride. The color of square represented the R-value of Spearman's correlation between top 50 genera and these parameters. One asterisk indicated $0.01 < P < 0.05$; Two asterisks indicated $0.001 < P < 0.01$; Three asterisks indicated $P < 0.001$.

4. Discussion

Excessive salt intake is a well-known trigger of hypertension, yet its effects on lipid metabolism and gut microbiota remain poorly understood. While prior studies in mice and rats have explored how insufficient or excessive salt affects lipid metabolism, its specific impact on cholesterol metabolism is still unclear. Hamster, a robust model for cholesterol research, was used in this study to examine how salt intake

levels from 0.4 to 24 g/kg influence cholesterol metabolism and gut microbiota. The AIN-93M rodent diet, containing 0.11% sodium (equivalent to 3 g/kg NaCl), served as the baseline. Six doses were tested: 0.4 g/kg (1/8X), 0.8 g/kg (1/4X), 3 g/kg (1X), 6 g/kg (2X), 12 g/kg (4X), and 24 g/kg (8X).

Results showed that salt intake, whether below (< 3 g/kg) or above (> 3 g/kg) the baseline, did not affect plasma levels of total cholesterol (TC), triglycerides (TG), HDL-C, non-HDL-C, or the non-HDL-C/TC ratio (Table 2). This aligns with the results described in a meta-analysis by He and MacGregor [23], who found no significant lipid changes across three trials, as well as with those of Harsha et al [24] and Uetake et al [25], who reported similar stability in blood lipids despite sodium variations. Higher salt doses increased water consumption in hamsters but left blood glucose, food intake, body weight, and organ weights unchanged (Table 1).

The liver is one of key sites of lipid metabolism. Salt intake below 3 g/kg had no significant effect, but above 3 g/kg, it caused a dose-dependent rise in cholesterol and total hepatic lipids (Fig. 1). While animal studies on this link are lacking, clinical evidence ties a high salt intake to NAFLD. Choi et al. [7], Huh et al [8], and Lanaspa et al. [26] reported higher NAFLD prevalence with increased sodium intake, suggesting that excessive salt promotes liver lipid accumulation, consistent with our findings.

Emerging evidence indicates that high-salt diets may influence host health and disease through gut microbiome modulation. For instance, a previous study demonstrated that high salt intake could exacerbate murine colitis by reducing *Lactobacillus* abundance and butyrate production [27]. Similarly, high salt consumption has been shown to decrease beneficial *Lactobacillaceae* levels and the gut microbiota metabolite 5-HIAA, thereby worsening prostatitis [28]. In the present study, gut microbiota analysis revealed no phylum-level changes across the 0.4–24 g/kg range, but the significant shifts occurred at family and genus levels (Figs. 5). Dominant families in hamsters included *Erysipelotrichaceae*, *Ruminococcaceae*, *Eubacteriaceae* (*Firmicutes*), and *Bacteroidales S24-7* (*Bacteroidetes*). Salt intake from 0.4 to 24 g/kg progressively reduced *Erysipelotrichaceae* abundance, while *Ruminococcaceae* increased dose-dependently (Fig. 5). At the genus level, higher salt intake markedly decreased the abundance of *Allobaculum* (within *Erysipelotrichaceae*), a trend consistent with Yoshimura et al. [29], who noted depleted *Allobaculum* in ApoE-deficient mice fed 4% NaCl. Other studies link reduced *Allobaculum* abundance to excessive metal ions, such as iron [30] and copper [31, 32], suggesting a similar trend with high salt intake. Conversely, salt intake above 6 g/kg dose-dependently increased the abundance of *norank_f_Ruminococcaceae* (within *Ruminococcaceae*). These results highlight that salt dosage significantly reshapes gut microbiota composition at finer taxonomic levels.

SCFAs (acetic, propionic, and butyric acids; 60:20:20 ratio), vital microbial fermentation, support health benefits by improving the lipid metabolism [17, 33-35]. We found that increasing salt intake progressively lowered fecal SCFAs concentrations, particularly acetic acid, the most abundant SCFA (Fig. 3). Similarly, spontaneously hypertensive rats consistently showed significantly lower concentrations of acetate than normotensive *Wistar Kyoto* rats [36]. *Allobaculum* was reported to be a SCFA producer [37].

Spearman's correlation analysis (Fig. 6) confirmed a strong positive link between *Allobaculum* abundance and acetic acid levels, but not with other SCFAs, supporting its role as an acetate producer, though some suggest it generates butyrate [38]. Fecal levels of SCFAs also correlated positively with *Desulfovibrio* and *Parasutterella* abundance and negatively with *norank_f_Ruminococcaceae* and others (Fig. 6), indicating that high salt intake alters microbial structure and reduces the production of SCFAs.

The decrease in the production of SCFAs may be related to an increase in liver lipid concentrations. SCFAs are known to suppress hepatic lipid accumulation [39, 40], and their reduction with high salt intake (leading to low fecal SCFA levels) likely promotes lipid buildup. However, lower fecal SCFA concentrations could reflect increased absorption into the liver [41], where acetate—a substrate for lipogenesis and cholesterol synthesis [42, 43]—may drive lipid accumulation. Spearman's analysis (Fig. 6) showed hepatic cholesterol and fatty acid levels negatively correlated with *Allobaculum* and *Bacteroides* abundance, and positively with *norank_f_Ruminococcaceae* and others, though the mechanisms remain unclear. Given *Allobaculum*'s SCFA-producing role, high salt-induced gut microbiota shifts likely contribute to the elevation of liver lipids.

Altering salt intake had minimal impact on plasma lipid concentrations but it led to hepatic cholesterol accumulation at high doses, potentially linked to reduced fecal sterol excretion. Excess cholesterol is typically cleared through two pathways [44, 45]. First, unabsorbed cholesterol is excreted directly in feces, with some converted by gut microbiota in the large intestine into metabolites like coprostanol, coprostanone, and dihydrocholesterol, which, along with neutral sterols, are then eliminated. Second, cholesterol is transformed in the liver into primary bile acids—cholic acid (CA) and chenodeoxycholic acid (CDCA)—some of which are further metabolized by gut microbiota into secondary bile acids, lithocholic acid (LCA) and deoxycholic acid (DCA), before fecal excretion. In this study, fecal lipid analysis revealed that salt doses of 0.4–12 g/kg had comparable effects on neutral and acidic sterol concentrations, whereas 24 g/kg significantly reduced both (Fig. 2). This suggests that high salt intake may drive liver lipid accumulation by impairing fecal sterol excretion.

Spearman's correlation analysis (Fig. 6) further indicated links between fecal sterol levels and gut microbiota. Total neutral sterol concentrations positively correlated with the abundance of *Allobaculum*, *Bacteroides*, *Prevotellaceae_Ga6A1_group*, and *unclassified_p_Firmicutes*, consistent with findings in hamsters [18]. Total acidic sterol levels showed positive correlations with *Allobaculum* and *Bacteroides*, and negative correlations with *Bifidobacterium* and *Helicobacter*, aligning with Midtvedt [45], who implicated *Bacteroides* and *Bifidobacterium* in bile acid metabolism. These results suggest that salt intake modifies gut microbiota involved in sterol metabolism. High salt consumption likely elevates hepatic cholesterol by altering SCFA-producing microbiota, reducing sterol excretion, and promoting lipid retention in the liver.

The present study has several limitations. First, although murine models were used for experimentation, the gut microbiota composition in hamsters differs significantly from that in humans. Thus, the precise effects of dietary salt on human gut health and microbiota modulation require further validation among population.

Second, while dietary salt was shown to reshape the microbial community across taxonomic levels (from phylum to genus), the exact mechanisms by which salt specifically influences gut microbiota composition and the molecular targets of its metabolites require deeper investigation. Future studies could employ *in vitro* fermentation and RNA-sequencing to elucidate the underlying mechanisms of high salt-induced microbiota alterations.

5. Conclusions

In summary, we found that excessive salt intake markedly increased the concentration of liver lipids in hamsters, although it did not alter the concentration of plasma lipids. In addition, excessive salt intake dose-dependently reduced the relative abundance of *Allobaculum*, concomitant with a reduction in fecal concentrations of SCFA. Further correlation analyses showed a positive link between the relative abundance of *Allobaculum* and concentrations of SCFA. It was therefore concluded that excessive salt consumption might increase hepatic lipid accumulation by modulating the abundance of SCFA-producing gut microbiota.

Conflict of interest

The authors declare there is no conflict of interest.

Acknowledgments

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