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Alterations of gut microbiota and cytokines in elevated serum diamine oxidase disorder

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Abstract

The present study aimed to explore gut microbiota alterations and host cytokine responses in a population with elevated serum diamine oxidase (DAO) disorder. A total of 53 study participants were included in this study, segregated into 2 groups: subjects with high-level DAO (DAO-H, n = 22) subjects with normal DAO level (DAO-N, n = 31). We investigated the clinical and demographic parameters of study participants. The fecal bacterial communities and serum cytokines in 2 groups were assessed by 16S ribosomal RNA gene sequencing and immunoassay. High-pressure liquid chromatography was used to determine hemoglobin Alc. Flow cytometry was used to find the cytokine level in the blood serum. There is no difference in age, total cholesterol (TCHO), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), hemoglobin Alc, fasting plasma glucose (FPG) and homocysteine between the 2 groups. No significant difference were found in α-diversity between the 2 groups, however, the gut microbiota of subjects in DAO-H were characterized by marked interindividual differences, decreased abundance of Phocaeicola, Lachnospira, Bacteroides, Alistipes, Agathobacter, Lachnospira and Bactetoides and increased abundances of Mediterraneibacter, Blautia, Faecallibacterium, Agathobacter, and Parasutterella. Furthermore, the cytokines were no related to the DAO level in both groups and exhibited no significant differences between DAO-H and DAO-N. This study adds a new dimension to our understanding of the DAO and gut microbiota, and revealed that an increase in the DAO level in the intestinal mucosa could alter the gut microbiota composition, which can cause gut-related complications. Research is needed to extensively evaluate downstream pathways and provide possible protective or treatment measures pertaining to relevant disorders.

Abbreviations: ANOVA = analysis of variance, Ct = cycle threshold, DAO = diamine oxidase, DAO-H = high-level DAO, DAO-N = DAO-normal, FPG = fasting plasma glucose, HDL-C = high density lipoprotein cholesterol, HbA1c = hemoglobin Alc, IFN-α = interferon-alpha, IFN-γ = interferon-gamma, IL = interleukin, LDA = linear discriminant analysis, LDL-C = low density lipoprotein cholesterol, PCoA = principal coordinates analysis, PERMANOVA = permutational MANOVA, TCHO = total cholesterol, TG = triglyceride, TNF = tumor necrosis factor.

Keywords: 16S rRNA gene sequencing, cytokine, diamine oxidase, gut microbiota

1. Introduction

Impairments in the intestinal mucosal barrier manifest as increased intestinal permeability.[1] Diamine oxidase (DAO) is an intracellular enzyme in the intestinal epithelium, when the permeability of the intestine abnormally increased duo to some sort of disruption, DAO in the lumen quickly pass through the intestinal mucosa and into the peripheral blood. DAO was an essential indicator of intestinal mucosal barrier function. The damage to the intestinal mucosal barrier can easily lead to the migration of intestinal bacteria and the invasion of toxins, which can cause multiple organ dysfunction syndromes in severe cases.[2]

DAO is primarily found in mature villous cells at their apical ends in both humans and animals. Its activity represents the strength and maturity of the small intestine mucosa. Numerous human and animal studies have shown that there is inverse relationship between DAO activity in serum and small intestine permeability.[3]

Intestinal mucosal barrier injury was associated with increased DAO levels. DAO is acritical enzyme that catalyzes histamine oxidation, mainly produced by small intestine villous epithelial cells. DAO activity reflects the function of the small intestine, and a large amount of DAO will be released when the small intestine villous epithelial cells are damaged. Under normal circumstances, serum DAO level is stable, but serum DAO level will increase when the intestinal mucosal barrier is damaged.[4]

Previous studies have demonstrated that the increased production of inflammatory cytokines harms the intestinal mucosal

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

All participants provided informed consent and the institutional ethics board approved the study of PLA Strategic Support Force Medical Center.

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barrier and epithelial function.[5,6] There are few studies on the relationship between DAO level in the human body, intestinal microbiota structure and the abundance of related probiotics at home and abroad. Moreover, the limited related studies are primarily from rodent experiments. The relationship between serum DAO, cytokines, and intestinal flora is still under discussion.

Hence, we designed and conducted a cohort study of high-level DAO (DAO-H) and DAO-normal (DAO-N) populations. In this study, the full-length 16S rRNA gene sequencing technology was used to analyze the genomes of fecal bacteria from 22 DAO-high and 31 DAO-N participants for exploring the alterations of gut microbiota. and then the host cytokines responses in a population with elevated serum DAO disorder. This study provides the characteristics of intestinal microflora distribution and cytokine level in people with high serum DAO in vivo, opens ideas, and lays a foundation for finding intestinal micro-ecological regulation means to reduce DAO, such as probiotics treatment.

2. Methods

2.1. Cohort and study design

Participants recruited during 2020 from Physical Examination Center in PLA Strategic Support Force Medical Center. A total of 53 participants were included in this study, comprising 22 with high DAO (DAO-H group) and 31 age- and sex-matched control subjects with normal DAO (DAO-N group). The study flow chart was depicted in Figure 1. All participants provided informed consent and the institutional ethics board approved the study of PLA Strategic Support Force Medical Center. DAO-H was diagnosed according to DAO over 8 U/L.

Inclusion criteria: Age ≥ 18 and ≤ 65; Permanent residence is Beijing. Exclusion criteria: History of intestinal microbiota disorder caused by severe gastrointestinal diseases; Antibiotics or probiotics or other drugs seriously affect the daily intestinal microbiota structure within 1 month; Pregnant or lactating women; Patients with recent diarrhea and constipation; Acute infections, malignant tumors, acute and chronic liver diseases, and autoimmune diseases; Those who cannot carry out the informed consent process or are unwilling to join the study.

2.2. Detection of increased intestinal permeability

2.2.1. Determination of DAO. Three milliliter of fasting venous blood from 53 subjects was collected with a coagulation booster tube and centrifuged at 1000 × g for 15 minutes. Serum was separated and all tests were completed within 4 hours after sample collection. DAO was detected by JY-DL biochemical index analyzer (Beijing Zhongsheng Jinyu Diagnostic Technology Co., Ltd.) and supporting reagent (enzyme method). All operations are carried out strictly accordance with the instrument and reagent instructions.

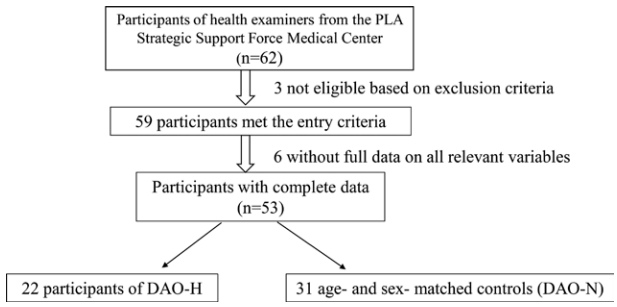

Figure 1. The flowchart of the selection of participants for the study. DAO = diamine oxidase, DAO-H = high-level DAO, DAO-N = DAO-normal.

2.3. DNA extraction from stool samples

5.0 g of fresh stool samples from 53 subjects were collected using sterile utensils, stored in sterile frozen test tubes, sealed and sent to the laboratory of Institute of Microbiology, Chinese Academy of Sciences, within 1 hour.

The total bacterial DNA was extracted from stool samples of all subjects using Kit KAPA HiFi HotStart DNA Polymerase (Biozeron, Shanghai, China), according to the manufacturer's instructions. The taxa of the gut microbiota were determined by specific primers.

The relative abundance of gut bacteriawas quantified using cycle threshold values and expressed in relative expression units per 200 mg of stool.

2.4. 16s Ribosomal RNA gene amplicon and sequencing

We used universal primers linked with indices and sequencing adaptors to amplify the full-length regions of the bacterial 16S ribosomal RNA (16S rRNA) gene after extracting of total DNA from the stool samples. The amplicons were sequenced on a QuantiFluor™ -ST platform to obtain 300-bp paired-end reads and for taxonomic assignment. Detailed descriptions of the amplicons and the sequencing analysis protocol are provided in Figure 2.

2.5. Determination of biochemical indicator

Total cholesterol (TCHO) was determined by the CHOD-POD method, high density lipoprotein cholesterol (HDL-C) by direct select-selection agreement method, low density lipoprotein cholesterol (LDL-C) by direct method-surfactant elimination method, triglyceride (TG) by Gpo-PAP method and plasma glucose by glucose oxidase method. hemoglobin Alc (HbA1c) was determined by high pressure liquid chromatography.

2.6. Measurement of plasma cytokine levels by a multiplex immunoassay

Approximately 2 mL of peripheral blood were collected from all subjects with DAO-H and healthy individuals in gel tube with clot activator. After collection, samples were incubated at room temperature for 30 minutes and centrifuged at 1000g for 10 minutes. The supernatant was withdrawn, and the serum was used for cytokine quantification by the multiplex bead-based flow fluorescent immunoassay (Raisecare, Qingdao, China). The levels of interleukin (IL) -1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-10, IL-12, IL-17A, interferon-alpha (IFN-α), interferon-gamma (IFN-γ), and tumor necrosis factor (TNF)-α were detected. Results were analyzed by LEGEND plex 8.0 software and expressed in pg/mL.

2.7. Statistical analysis

The clinical parameters were analyzed using an unpaired Student *t* test. comparisons between groups were performed with Student t tests and chi-square tests for quantitative and categorical variables, respectively. Variables that followed a Gaussian distribution were compared with 2-tailed *t* tests or analysis of variance (ANOVA). We tested the homogeneity of variances by using Levene's test. The 2 groups were compared with nonparametric Mann–Whitney *U* test for variables that violated the assumptions of normality or homoscedasticity.

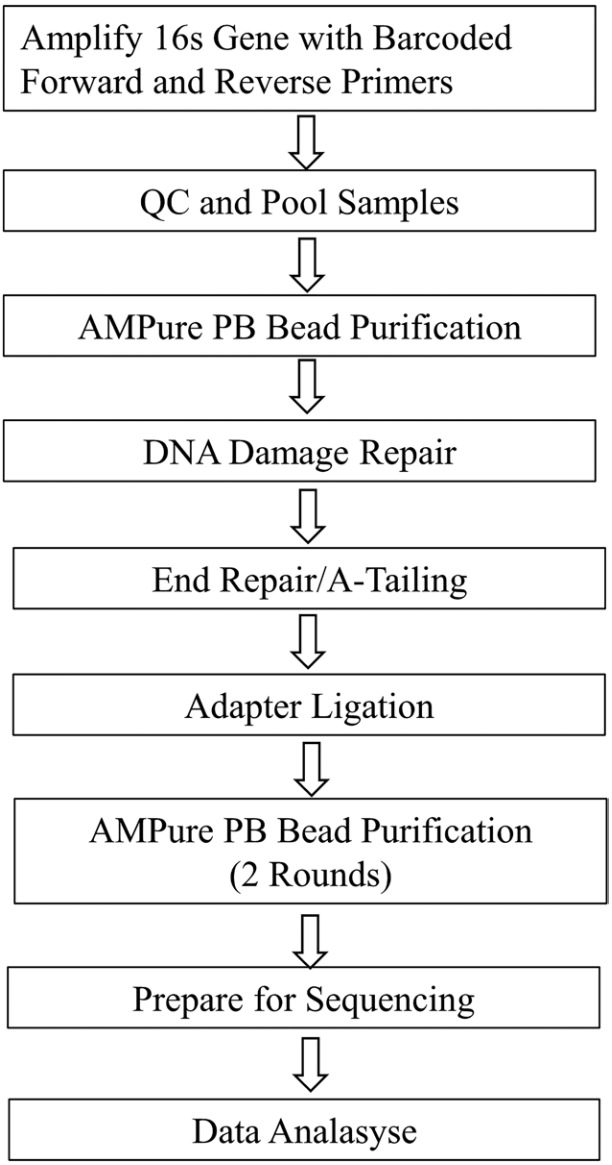

Figure 2. Amplicons and sequencing analysis protocol.

3. Result

3.1. Clinical characteristics of DAO-h and DAO-n groups

The demographic and clinical information of 22 subjects with high DAO and 31 DAO-N subjects enrolled in Table 1. There was no difference in age, TCHO, TG, HDL-C, LDL-C, HbA1c, fasting plasma glucose (FPG) and homocysteine between the 2 groups.

3.2. Subjects with DAO-h have altered and more diverse gut microbiota

3.2.1. The characteristics of the gut microbiota in the 2 groups. We measured the bacterial richness within each sample from both the DAO-H and DAO-N using 3 different methods, the observed number of operational taxonomic units, the Chao1 diversity index, and the Shannon entropy index. The bacterial gut microbiota from patients with DAO-H was not more diverse than those from DAO-N by all the 3 estimators ($P = .23$ for the Chao1 diversity index, $P > .74$ for the observed species diversity index, and $P = .40$ for the Shannon index; by Wilcoxon rank-sum test, Fig. 3a).

We calculated the β-diversity of the gut microbiota using the weighted UniFrac distances and the Bray-Curtis (dissimilarity) to identify possible differences between the bacterial components in the gut microbiota of subjects from the DAO-H and DAO-N groups. The principal coordinates analysis (PCoA) showed that the gut microbiota of subjects with high DAO was distinct from those of DAO-N groups, but had no statistical difference ($P < .66$) by a Permutational MANOVA (PERMANOVA) implementation using Uni-Frac distances and Bray-curtis dissimilarity, Fig. 3b). These findings indicate that the richness and diversity of the gut microbiota in patients with DAO-H are no different from that of DAO-N groups.

3.3. Alterations of the gut microbiota between DAO-h and DAO-N

A supervised comparison of the microbiota between the DAO-H and DAO-N groups was performed by linear discriminant analysis (LDA) effect size (LEfSe) analysis without any adjustments. We used a logarithmic LDA score cut off 2.0 to identify important taxonomic differences between the DAO-H and DAO-N and found a notable difference in fecal microbiota between the DAO-H and DAO-N groups based on LDA LEfSe analysis (Fig. 4). We observed that the relative abundance of Phocaeicola, Bacteroides, Lachnospira, Alistipes, Agathobacter, Lachnospira and Bactetoides decreased in the DAO-H group, while the relative abundances of Mediterraneibacter, Blautia, Faecallibacterium, Agathobacter, and Parasutterella increased significantly, (LDA score (log10) > 2, Fig. 4).

3.3.1. Systemic cytokine profile in subjects with DAO-h was similar to DAO-N. To investigate whether the alterations of intestinal microbiota impacted on systemic cytokine profile in patients with DAO-H, we analyzed the serum concentrations of IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-10, IL-12, IL-17A, IFN-α, IFN-γ, and TNF-α by flow cytometer. We did not detect significant differences in these cytokines ($P > .05$) (Table 2).

4. Discussion

The present study, a similarity was observed between DAO-H and DAO-N. The demographic and clinical parameters of 22 patients based on DAO-H and 31 DAO-N individuals have revealed that there was no significant variance in age, TCHO, TG, HDL-C, LDL-C, HbA1c, FPG, and homocysteine. The TG was profoundly higher in DAO-H whereas, HDL-C was higher in DAO-N. However, the β-diversity revealed that there was a significant variation between DAO-H and DAO-N individuals. Gut microbiota of subjects in DAO-H were characterized by marked interindividual differences, decreased abundance of Phocaeicola, Lachnospira, Bacteroides, Alistipes, Agathobacter, Lachnospira and Bactetoides and increased abundances of Mediterraneibacter, Blautia, Phocaeicola, Faecallibacterium, Agathobacter, and Parasutterella.

Histamine intolerance is a disturbance in the histamine homeostasis due toa reduced intestinal histamine degradation, mostly caused by a defect in the DAO.[7] Histamine, putrescine, and cadaverine are a few examples of the diamines that can be oxidized by the enzyme DAO. DAO deficiency may be caused by a genetic mutation or connected to common diseases, particularly inflammatory or degenerative intestinal conditions, that restrict the secretion of this enzyme.[8] The DAO is possibly linked with the gut dysbiosis and effect gut bacterial structural and composition.[9]

The profound decrease of α-diversity with an increase in infection has been studied using 16S rRNA sequencing,[10,11] and metagenomic sequencing by 16S rRNA.[12] This study analyzed the gut bacterial diversity using metagenomics targeted 16S rRNA. The α-diversity was initially measured based on Choa1 index (abundance) and Shannon (evenness). However, previous

Table 1

Comparison of clinical characters between the 2 groups (x ± s).

Group	n	Age (yr)	TCHO	TG	HDL-C
DAO-N	31	44.5 ± 5.9	4.76 ± 0.73	1.27 ± 0.72	1.74 ± 0.28
DAO-H	22	44.3 ± 7.4	4.85 ± 0.82	1.55 ± 0.79	1.72 ± 0.26
t		0.098	−0.428	−1.000	0.310
P		0.922	0.671	0.322	0.758
Group	n	LDL-C	HbA1c(%)	FPG	Hyc
DAO-N	31	2.64 ± 0.56	5.56 ± 0.29	5.53 ± 0.49	11.60 ± 2.48
DAO-H	22	2.74 ± 0.65	5.55 ± 0.28	5.59 ± 0.41	12.62 ± 2.76
t		−0.541	0.139	−0.512	−1.398
P		0.591	0.890	0.611	0.168

DAO-H = high-level DAO, DAO-N = DAO-normal, FPG = fasting plasma glucose, HDL-C = high density lipoprotein cholesterol, Hyc = homocysteine, HbA1c = hemoglobin Alc, LDL-C = low density lipoprotein cholesterol, TCHO = total cholesterol, TG = triglyceride.

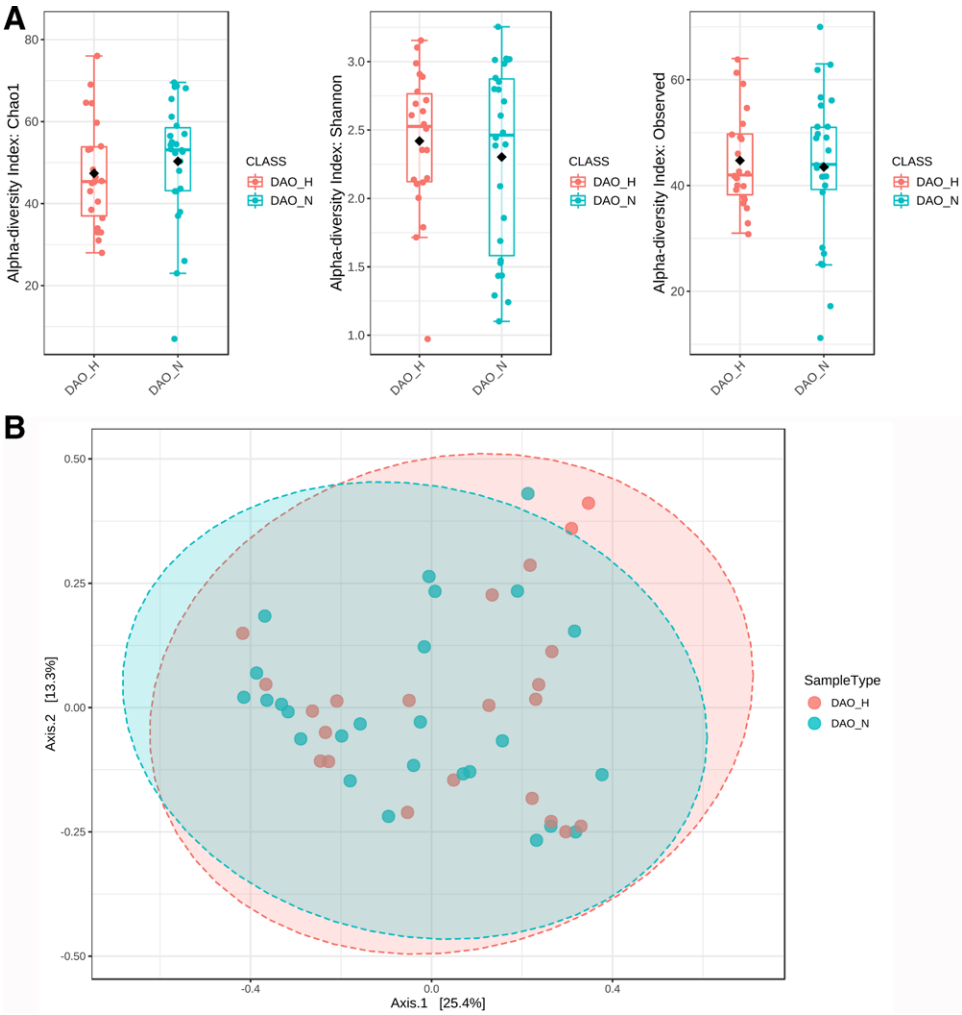

Figure 3. The α-diversity and β-diversity indices of the fecal microbiome in the DAO-H and DAO-N groups. a Box plots depict differences in the fecal microbiome diversity indices between the DAO-H and DAO-N groups according to the Chao 1 index, observed species index, and Shannon index based on OTU counts. Each box plot represents the median, interquartile range, minimum, and maximum values. OTU: operational taxonomic units (b) PCoA plots of bacterial β-diversity based on the weighted UniFrac distance and Bray-curtis dissimilarity analyzed according to health status. Patients with DAO-H and age-matched DAO-N groups are colored in green and red, respectively. DAO-H = high-level DAO, DAO-N = DAO-normal, PCoA = principal coordinates analysis.

study calculated the α-diversity using different indices such as, Chao1, Shannon, and Simpson.[13] The abundance and evenness in this study were not much different. which means that the DAO has not significant effect on gut bacterial diversity.

The result of the PCoA showed no significant differences between DAO-H and DAO-N. However, 25.4% distribution on Axis 1 and 13.3% distribution on Axis 2 were observed.

Moreover, the PERMANOVA analysis shown that there was strong covariance and weak correlation between DAO and gut bacterial diversity ($R^2 = 0.016$). In contrast, a previous study revealed and obtained significant difference based on β-diversity between DAO-N and DAO-H groups using multidimensional scaling by PCoA,[14] this difference may be related to the small sample size of this study.

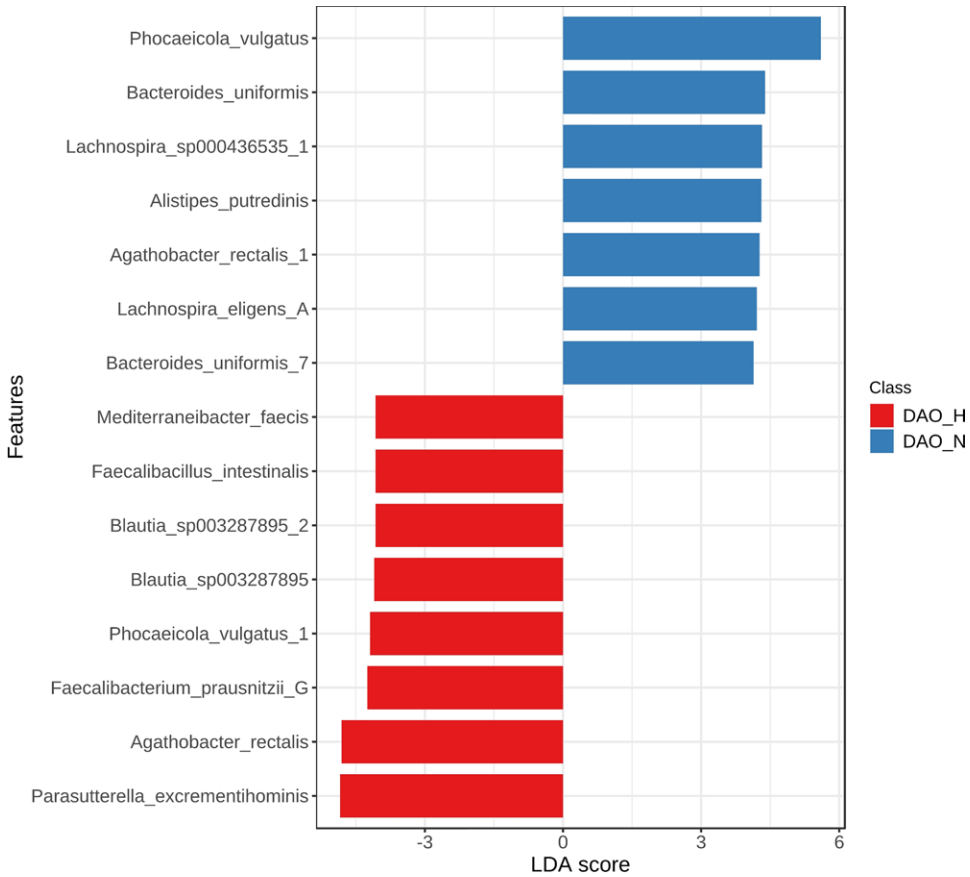

Figure 4. Taxonomic differences of fecal microbiota in DAO-H and DAO-N. a Linear discriminant analysis (LDA) effect size (LEfSe) analysis revealed significant bacterial differences in fecal microbiota between the DAO-N (positive score) and DAO-H groups (negative score). LDA scores (log10) > 2 and $P < .05$ are shown. DAO-H = high-level DAO, DAO-N = DAO-normal.

Furthermore, we analyzed gut microbe differences in 2 groups by using the LEfSe analysis based on LDA, shown in Figure 4. A total 16 operational taxonomic units were assigned to 16 species. No significant differences were observed at levels of phylum, class, order, family.

This study found that Parasutterella increased in DAO-H group. Parasutterella, a genus of Betaproteobacteria, has been defined as a member of the healthy fecal core microbiome in the human gastrointestinal tract.[15] In humans, the genus of Parasutterella has a unique phylogenetic classification as it stands out as one of the most frequently reported taxa within the class Betaproteobacteria in the gut, The relative abundance of this species has been associated with different host health outcomes such as inflammatory bowel disease, obesity, diabetes, and fatty liver disease.[16,17] Parasutterella produces succinate as a fermentative end-product.[18] Succinate, as one of the key intermediate metabolites produced by gut microbiota, plays an important role in cross-feeding metabolic pathways.[15] The capacity of Parasutterella to produce succinate indicates 1 potential way Parasutterella supports interspecies metabolic interactions within the gut ecosystem. Succinate causes an increase in intestinal permeability, this may be related to elevated DAO.

This study found that Bacteroides decreased in DAO-H group. As gut commensals, Bacteroides play multiple roles;

Table 2

Comparison of cytokines between the 2 groups [M (25^{th},75^{th})].

Cytokines	DAO-H	DAO-N	Z	*P*
IL-1	8.28 (4.11, 15.11)	8.28 (3.71, 14.64)	−0.464	.643
IL-2	1.78 (1.30, 2.40)	1.89 (1.37, 2.35)	−0.423	.672
IL-4	2.40 (1.62, 3.77)	2.11 (1.84, 3.31)	−0.065	.948
IL-5	3.17 (2.24, 4.35)	2.85 (2.04, 3.88)	0.781	.435
IL-6	6.86 (5.22, 10.94)	7.86 (6.28, 12.73)	−0.838	.402
IL-8	35.56 (0, 126.14)	12.69 (0, 51.40)	−1.006	.315
IL-10	1.81 (1.44, 1.94)	1.74 (1.53, 2.11)	−0.326	.745
IL-12	0.37 (0.15,0.94)	0.37 (0.15, 0.91)	−0.089	.929
IL-17A	5.18 (3.60, 7.46)	4.55 (3.48, 8.38)	−0.187	.852
IFN-α	2.07 (1.63, 3.03)	1.96 (1.58, 2.91)	−0.553	.580
IFN-γ	7.17 (6.16, 10.70)	5.70 (4.77, 8.77)	−1.366	.172
TNF-α	2.28 (1.12, 3.81)	2.07 (1.35, 3.94)	−0.163	.871

DAO-H = high-level DAO, DAO-N = DAO-normal, IL = interleukin; IFN-α = interferon-alpha; IFN-γ = interferon-gamma; TNF-α = tumor necrosis factor-alpha.

they can provide protection from pathogens and supply nutrients to other microbial residents of the gut. Past research has revealed that mucin-type O-glycans are important contributors to their mutualistic roles and directly impact the interaction of Bacteroides spp with host tissues.

DAO deficiency has been linked to single-nucleotide polymorphisms that encode a protein with decreased histamine breakdown capacity and may have hereditary roots.[19] On the other hand, impaired DAO activity can also be transient and reversible and can result from a side effect of several commonly used pharmaceuticals, such as clavulanic acid or acetylcysteine might be a secondary sign of digestive issues. Due to these digestive issues, the DAO might be a significant factor that cause gut bacterial dysbiosis, which could alter the structural and composition of bacterial diversity in the gut.

Inflammatory cytokines are known to contribute to intestinal damage.[5] Various mechanisms that favor a tolerogenic immune response maintain segregation between the host gut epithelium and the microbiome at homeostasis. In the small intestine, this is achieved primarily by PRRs, antimicrobial peptides and secreted IgA, and an immune milieu consisting of a cytokine environment that includes IL-33, IL-10 and transforming growth factor-β (TGFβ).[19,20]

Parasutterella affects the immune response in the gut. Ju T et.al shows Parasutterella colonization did not alter the level of detected colonic cytokines except for a tendency to reduce the IL-1β expression, which indicates that the colonization of Parasutterella did not induce the host innate immune responses and further supports the role of Parasutterella as commensal or symbiotic gut microbe.[18] The results is consistent with our study.

This study also includes some limitations: the sample size of the study was too small and might affect the results of the study. Further research with a larger sample size is needed to evaluate the effect of high DAO on gut microbiota and cytokines.

In conclusion, differences in gut microbiome composition and diversity are shown to be linked to DAO level in the gut mucosal membrane. This study provides the characteristics of intestinal microflora distribution and cytokine level in people with elevated serum DAO, broaden our knowledge on DAO in the intestinal mucosal barrier and lays a foundation for finding intestinal microecological regulation means to reduce DAO, such as probiotics treatment.

Author contributions

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Writing – review & editing: Haiying Jia.

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