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ORIGINAL RESEARCH

Imidazole Propionate is Increased in Diabetes and Associated with Stool Consistency

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Background: Imidazole Propionate (ImP) is a new marker of Type 2 diabetes mellitus (T2DM), which can induce impaired glucose metabolism and weaken the efficacy of metformin. An extensive exploration into literature suggests that ImP may be associated with stool consistency.

Purpose: Through an in-depth study of the relationship between stool consistency, bile acids, fecal microbiota and ImP, we intend to explore the mechanism driving the ImP content difference in T2DM.

Patients Under Study and Methods: This is a single-center, prospective, cross-sectional study. Plasma ImP and stool consistency were analyzed among 96 diabetic subjects and 45 healthy subjects. All subjects were divided into the stool consistency normal (N) group and the stool consistency abnormal group, of which the abnormal group was sub-divided into the hard stool (H) group and the soft stool (S) group. After identifying the correlation between ImP and stool consistency, we analyzed the influence of bile acids and fecal microbiota on ImP in diabetic subjects.

Results: For T2DM patients, the ImP level of the abnormal stool consistency group was significantly higher than that of the normal stool consistency group ($P < 0.001$). Results were verified in 45 healthy subjects ($P = 0.002$). ImP was significantly associated with taurocholic acid (TCA) ($P = 0.003$) in feces, taurodeoxycholate (TDCA) ($P = 0.003$), glycochenodeoxycholate (GCDCA) ($P = 0.021$), and glycocholic acid (GCA) ($P = 0.031$) in plasma. The Shannon index of Group N was significantly higher than that of Group H ($P = 0.041$) and Group S ($P = 0.003$).

Conclusion: ImP was higher in diabetic patients with abnormal stool consistency than in those with normal stool consistency, which was related to the proportion of bile acids and fecal microbial structure. These findings may improve our understanding of ImP and contribute to the treatment of T2DM by improving stool consistency.

Keywords: ImP, T2DM, stool consistency, bile acids

Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disease, which is closely related to the metabolites of intestinal microbiota. Some bacterial metabolites, such as branched chain amino acids,[1] secondary bile acids[2] and short-chain fatty acids,[3] can affect the condition of diabetes. The latest studies indicate that Imidazole Propionate (ImP), produced by intestinal microbiome through abnormal histidine metabolism,[4] is a new marker of T2DM.[5] ImP induces impaired glucose metabolism by activating the P38 γ -MTOR1-S6K1 signal and reduces the efficacy of metformin.[6] This is an important discovery in the study of diabetes and microbiology in recent years.[7,8] ImP levels in T2DM patients can vary by a hundredfold, and studies have shown significant differences of ImP levels among T2DM patients, which is related to inflammation, diet, and intestinal microflora composition.[9,10]

In 1972, it was discovered that ImP would increase with the onset of gastrointestinal symptoms and decrease with improvement of such symptoms.[11] A recent study has discovered that for patients with irritable bowel syndrome, there is

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a significant increase in their ImP.[12] One of the symptoms exhibited by irritable bowel syndrome is the change in stool consistency, which has a strong influence on intestinal flora.[13,14] Therefore, we hypothesize that ImP differences in T2DM patients are closely related to stool consistency.

In this study, based on an examination of 96 T2DM subjects, we found that the ImP level of the abnormal stool consistency group was significantly higher than that of the normal stool consistency group. Results were verified in 45 healthy subjects. To explore the potential mechanism, we analyzed the factors that may affect fecal consistency: the bile acid and intestinal flora, and further looked into the relationship between these two factors and ImP.

Materials and Methods

Ethics Statement

This study has been approved by the Bioethics Committee of Beijing Friendship Hospital, Capital Medical University, with the ethical approval number of 2021-P2-140-1. The protocol used in this investigation is aligned to the principles expressed in the 1975 Declaration of Helsinki, which was revised in 2008. All participants have provided written informed consent.

Subjects

All patients and healthy individuals were recruited from Beijing Friendship Hospital, Capital Medical University. The inclusion criteria for T2DM patients were: Aged 18–75; conform to the diagnostic criteria of T2DM. The exclusion criteria were: Have a history of severe cardiovascular, respiratory, kidney, liver, gastrointestinal, blood or nervous system diseases; diabetic ketoacidosis, diabetic foot and other serious complications of diabetes; cognitive dysfunction. The inclusion criteria for healthy subjects were: Aged 18–75, without diabetes or abnormal glucose tolerance.

All patients were scored according to the Bristol stool scale (BSS), based on which, those scored 3, 4 were marked normal (N) and 1, 2, 5, 6 and 7 abnormal. Patients scored 1, 2 were classified as hard stool (H), and 5, 6 and 7 soft stool (S). According to the stool consistency, they were divided into two groups: the stool consistency normal (N) group and the stool consistency abnormal group (including Group H and Group S).

Imidazole Propionate Serum Measurements

To measure the imidazole propionate in a targeted manner, a plasma sample was extracted with 4 volumes of acetonitrile containing 5 ng/mL internal standard in a 1.5 mL polypropylene tube. After vortexing and centrifugation, 5ul of supernatant was injected into an Amide BEH column (2.1x100 mm, 1.7 mm particles; Waters), as well as acetonitrile and 10 mM ammonium acetate, which contained 10 mM ammonium acetate, 0.1% formic acid (phase A) and 10 mM using ammonium acetate. Gradient separation of 0.1% formic acid was conducted in 50% acetonitrile water (phase B). Mass spectrometry analysis was performed using Nexera X2 LC-30AD (Shimadzu Japan) and QTRAP 6500 (ABSCIEX, USA). The fragment ions 141.1/123.1 and NN dimethylphenylalanine internal standard 194/148.1 were optimized, and the imidazole propionate in the positive mode of multiple reaction monitoring was detected. The calibration curve of imidazole propionate was made in water and processed in the same way as the sample.

Bile Acids Measurements

To measure bile acids in a targeted manner, plasma samples were extracted with four times the volume of acetonitrile, and feces samples were extracted with three times the volume of methanol, containing 50 ng/mL internal standard in a 1.5 mL polypropylene tube. After vortexing and centrifugation, the supernatant was diluted with water and 10ul was injected into a C18 BEH column (2.1x100 mm, 2.5um particles; Waters, USA) and used with 0.1% formic acid in acetonitrile (phase A) and containing 0.1% formic acid in water (phase B), gradient separation. ACQUITY UPLC I-Class (Waters, USA) was used, coupled with QTRAP 4500 (ABSCIEX, USA) for mass spectrometry. The ion LCA 375.3/375.3; UDCA 391.4/391.4; HDCA 391.3/391.3; CDCA 391.3/391.3; DCA 391.3/391.3; CA 407.2/407.2; GUDCA 448.3/74.1; GCDCA 448.4/74.1; GDCA 448.3/74.2; GCA 464.3/74.1; TUDCA 498.3/80.1; TDCA 498.2/80.0; TCA 514.2/80.1 were optimized and detect bile acids were detected based on the nimodipine internal standard 417/122 by

multiple reaction monitoring negative mode. The bile acid calibration curve was made in water and processed in the same way as the sample.

Analysis of the Intestinal Microbial Community

DNA was extracted from about 100 mg of the feces. Then, the V3-V4 region of 16S rRNA was amplified using the primers 338F (5'-ACTCCTACGGGAGGCAGCA-3') and 806R (5'-GGACTACHVGGGTWTCTAAT-3'). The purified amplicons were constructed for single-end sequencing based on the IonS5TMXL sequencing platform. The reads were cut, filtered and then clustered into operational taxonomic units (OTUs) according to 97% similarity. The diversity analysis of gut microbiota included alpha and beta diversity analyses. The alpha-diversity is used to describe the richness and evenness of gut microbiota. The beta-diversity is used to analyze differences in the composition of gut microbiota. The UniFrac distances were used in Principal Coordinate Analysis (PCoA). Raw 16S rRNA data was public on NCBI with project ID SUB11371228.

Statistical Analysis

The ImP, age, blood glucose and other indicators of the enrolled subjects were represented by mean ± standard deviation. The Wilcoxon symbolic rank test was used to analyze the data of ImP, age, blood glucose and other indicators among the abnormal stool consistency group and normal stool consistency group.One-way ANOVA was used to compare the differences in ImP bile acids and Shannon index among the Group H, Group S and Group N. The cross-sectional multiple logistic regression was used to analyze the influence of blood glucose, bile acids and other factors on ImP. A P value of < 0.05 was regarded as statistically significant. Statistical analyses were performed using SPSS 25.0 and GraphPad Prism 8.0.

Results

Background Characteristics of the Subjects of Study

We recruited 96 patients with T2DM, 40 of whom had abnormal stool consistency (28 males and 12 females), including 22 in Group H and 18 in Group S, and 56 of whom had normal stool consistency (39 males and 17 females). We carried out an extensive collection of common diabetes indicators (Table 1). We measured ImP concentrations in fasting plasma samples from all of the 96 patients with T2DM. The ImP ranged from 1.25 nmol/L to 102.95 nmol/L.

The Relationship Between ImP and Stool Consistency

For T2DM patients, the ImP level of the abnormal stool consistency group was significantly higher than that of the normal stool consistency group ($P < 0.001$) (Figure 1A). Whether in Group H ($P < 0.001$) or Group S ($P = 0.002$) (Figure 1B), it was significantly higher than that in Group N. There was no significant difference between Group H and Group S ($P = 0.575$). In order to increase the credibility of the results, we performed multi-tests on the data, and the data of Group N and the abnormal stool consistency group were randomly and evenly divided into five parts, and four parts of each group were taken for testing each time, and a total of 25 tests were conducted. The results showed that the three tests $P = 0.001$ and the 22 tests $P < 0.001$ were consistent with the previous results. To avoid interference from other factors, the multiple regression analysis was conducted using ImP as the dependent variable and other indicators as independent variables. It was found that in addition to stool consistency, ImP was also significantly correlated with postprandial blood glucose ($P = 0.028$) (Table 2). In order to exclude the interference of blood glucose, we recruited another 45 healthy people, including 24 with normal stool consistency (ImP: 5.18±5.87 nmol/L) and 21 with abnormal stool consistency (ImP: 10.11±8.66 nmol/L). It was found that after the exclusion of the interference of blood glucose, ImP was still significantly correlated with stool consistency ($P = 0.002$) (Figure 1C).

ImP is Associated with Bile Acids

Bile acid is one of the indicators of stool consistency and easy to detect. In colon, CDCA and LCA activate TGR5 receptors on intestinal neurons,[15] thus increasing the permeability and peristalsis of intestinal mucosa and affecting the

Table 1 Patient Characteristics According to Stool Consistency

Characteristic	Stool Consistency (Normal) (n=56)	Stool Consistency (Abnormal) (n=40)	P value
ImP (nmol/L)	9.4±3.44	18.5±4.23	<0.001
Age (years)	54.8±3.27	60.0±3.19	0.017
Course of disease (years)	9.4±2.64	14.8±3.24	0.012
Weight (kg)	76.3±4.14	68.7±3.75	0.032
Height (cm)	169.5±3.12	168.2±8.16	0.491
BMI	26.3±2.04	24.4±4.12	0.031
Waist (cm)	95.4±3.47	92.1±3.52	0.116
Hip (cm)	98.5±3.02	97.1±3.04	0.376
Waist-hip ratio	1.0±0.25	0.9±0.25	0.147
Blood pressure (mmHg): systolic	129.8±5.35	130.8±4.43	0.456
Blood pressure (mmHg): diastolic	77.3±3.34	77.1±3.21	0.797
Capillary plasma glucose (mmol/L): fasting	7.3±1.55	7.4±2.78	0.854
Capillary plasma glucose (mmol/L): 2 h	16.0±2.07	15.2±2.03	0.419
Insulin (pmol/L): fasting	10.3±2.80	7.2±2.24	0.076
Insulin (pmol/L): 2 h	52.5±7.32	27.9±4.29	0.036
HbA1c (%)	8.8±1.40	8.8±1.34	0.928
HOMA-β	74.2±8.62	60.2±7.76	0.069
HOMA-IR	3.2±1.80	2.2±4.19	0.445
TC (mmol/L)	4.5±1.07	4.3±1.16	0.18
HDL (mmol/L)	0.9±0.46	1.0±0.50	0.314
LDL (mmol/L)	2.6±0.87	2.4±0.92	0.066
TG (mmol/L)	2.0±1.10	1.9±1.25	0.111

Abbreviations: ImP, imidazole propionate; BMI, body mass index; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglycerides; LDL, low-density lipoprotein cholesterol.

stool consistency.[16] It was found that LCA ≤ 30% or CDCA ≥ 5% in fecal bile acid was significantly related to abnormal stool consistency.[17] We detected 13 types of bile acids in the feces of 89 diabetic patients (19 of them belong to Group H, 16 Group S and 54 Group N). The results showed that the ImP level of subjects with LCA ≤ 30% was significantly higher than that of those with LCA > 30% ($P = 0.005$) (Figure 2A); subjects with CDCA ≥ 5% had significantly higher ImP levels than those with CDCA < 5%($P = 0.008$) (Figure 2B).

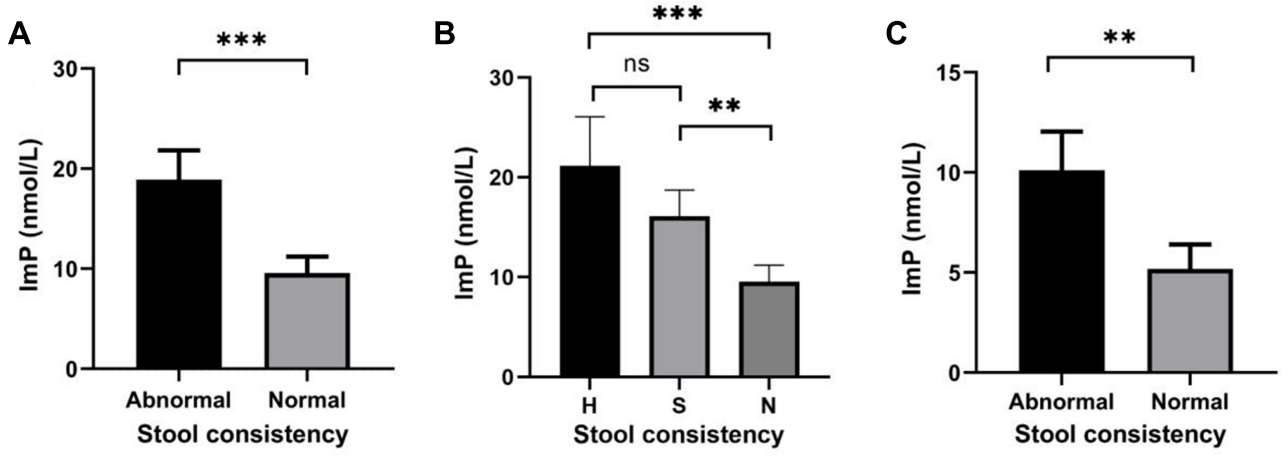

Figure 1 Imidazole propionate is associated with the stool consistency. (**A** and **B**) Plasma levels of imidazole propionate (ImP) in subjects with Type 2 diabetes divided according to the stool consistency. (**C**) Plasma levels of ImP in healthy subjects divided according to the stool consistency. $^{**}P < 0.01$, $^{***}P < 0.001$.
Abbreviations: H, hard; S, soft; N, normal.

Table 2 Multiple Logistic Regression Analysis of the ImP

Characteristics	Correlation	P value
Stool consistency Normal	−0.326	0.002
Stool consistency Hard	0.279	0.009
Capillary plasma glucose (mmol/L): 2 h (mmol/L)	0.249	0.020
Weight (kg)	−0.197	0.067
BMI	−0.178	0.100
Course of disease (years)	0.140	0.196
Insulin (uIU/mL): 2 h	−0.135	0.212
Blood pressure (mmHg): diastolic	0.135	0.213
Age (years)	0.129	0.233
Insulin (uIU/mL): fasting	−0.128	0.236
Stool consistency Soft	0.110	0.309
Capillary plasma glucose (mmol/L): fasting	0.109	0.316
HbA1c (%)	0.103	0.344
HOMA-IR	−0.099	0.362
HOMA-β	−0.083	0.446
Height (cm)	−0.081	0.457
LDL (mmol/L)	−0.080	0.460
Waist (cm)	−0.043	0.693
TC (mmol/L)	−0.039	0.718
HDL (mmol/L)	0.035	0.747
Blood pressure (mmHg): systolic	0.033	0.764
Waist-hip ratio	0.032	0.767
Sex Female	−0.031	0.772
Sex Male	0.031	0.772
Hip (cm)	−0.008	0.939
TG (mmol/L)	<0.001	0.999

Abbreviations: BMI, body mass index; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglycerides; LDL, low-density lipoprotein cholesterol.

Next, we analyzed the associations between 13 types of bile acids in feces and ImP. Surprisingly, the multiple regression analysis showed that only TCA was significantly associated with ImP ($P = 0.003$). Next, we detected 13 types of bile acids in the plasma of 96 diabetic patients and found that ImP was significantly correlated with TDCA ($P = 0.003$), GCDCA ($P = 0.021$) and GCA ($P = 0.031$) (Table 3).

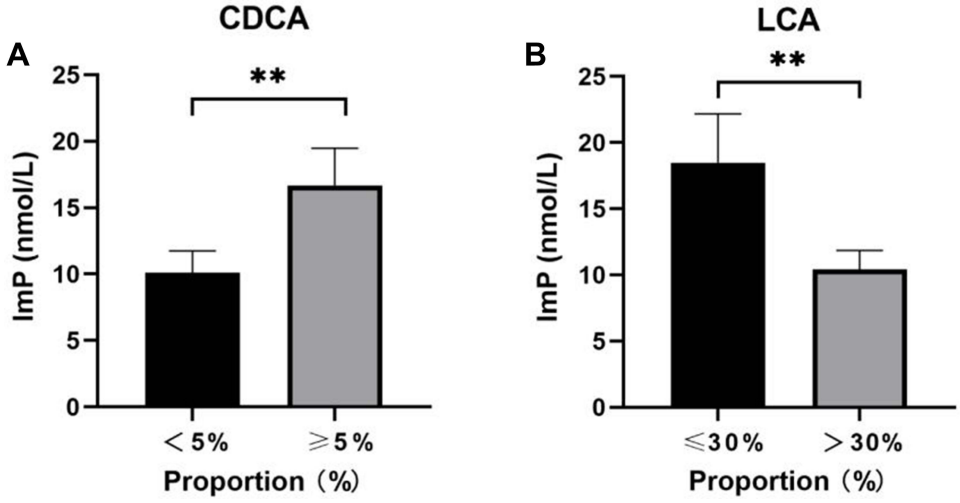

Figure 2 Imidazole propionate is associated with bile acids. (**A**) Imidazole propionate (ImP) level of subjects with LCA ≤ 30% was significantly higher than that of those with LCA > 30%. (**B**) Subjects with CDCA ≥ 5% had significantly higher ImP levels than those with CDCA < 5%. **$P < 0.01$.
Abbreviations: CDCA, chenodeoxycholic acid; LCA, lithocholic acid.

Table 3 Multiple Logistic Regression Analysis of the ImP and Bile Acids

Bile Acid	Correlation (Feces)	P value (Feces)	Correlation (Plasma)	P value (Plasma)
CA	−0.075	0.233	−0.003	0.015
CDCA	−0.03	0.59	−0.008	0.836
DCA	0.022	0.399	0.007	0.394
LCA	0.006	0.415	−0.038	0.780
TUDCA	−0.141	0.091	0.694	0.633
HDCA	−0.056	0.328	−0.025	0.111
GUDCA	0.441	0.074	−0.015	0.755
GDCA	−0.019	0.414	−0.013	0.501
TDCA	0.006	0.421	0.221	0.003
UDCA	0.017	0.056	0.012	0.468
GCDCA	0.096	0.096	0.020	0.021
GCA	−0.083	0.086	−0.040	0.031
TCA	0.102	0.003	0.0140	0.440

Abbreviations: CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; LCA, lithocholic acid; TUDCA, tauroursodeoxycholic acid; HDCA, hyodeoxycholic acid; GUDCA, glycoursodeoxycholic acid; GDCA, glycodeoxycholic acid; TDCA, taurodeoxycholate; UDCA, ursodeoxycholic acid; GCDCA, glycochenodeoxycholate; GCA, glycocholic acid; TCA, taurocholic acid.

Analysis of the Fecal Microflora

In order to reduce intra-group differences, fecal microbes of 10 people in each group of H, S and N were detected. The ImP levels in Group H (20.45±10.13 nmol/L) and Group S (20.48±9.50 nmol/L) were significantly higher than those in Group N (3.83±1.74 nmol/L) ($P < 0.001$). The results showed that the Shannon index of Group N was significantly higher than that of Group H ($P = 0.041$) and Group S ($P = 0.003$) (Figure 3A), and there was no significant difference between Group H and Group S ($P = 0.45$). These three groups were separated into different clusters in the UniFrac PCoA (Figure 3B).

At the phylum level (Figure 3C), there were significant differences between Group N and Group H in *Firmicutes* ($P = 0.049$) and *Actinobacteria* ($P = 0.01$), while there were significant differences between Group H and Group S in *Actinobacteria* ($P = 0.019$). At the genus level (Figure 3D), there were significant differences between Group N and Group H in *Bifidobacterium* ($P = 0.001$) and *Blautia* ($P = 0.008$), while there were significant differences between Group H and Group S in *Bifidobacterium* ($P = 0.019$). There was no significant difference between Group N and Group S at the level of genus or phylum.

Discussion

In this study, 96 diabetic subjects were evaluated and a strong association was found between ImP and stool consistency. Results were verified in 45 healthy subjects. Studies have established that ImP is not only a marker of T2DM, but also a marker of other diseases with abnormal stool consistency, such as gastrointestinal diseases. As a classic example, the incidence of lung cancer among men is higher than that among women, not only because men are more prone to lung cancer for their gene expression, but also because men smoke more often than women do. Smoking is a very important risk factor for lung cancer. In addition, ImP can modulate fetal neuro development in mice,[18] suggesting that ImP may be closely related to the nervous system. Moreover, after a patient's oral administration of antibiotics to inhibit the growth of intestinal bacteria, the ImP of plasma will rise instead,[19] suggesting that ImP may have other ways of production. Our understanding of ImP may be still in the initial stage, and there are still many unknown areas for further exploration.

In order to clarify the mechanism behind the correlation between ImP and stool consistency, we conducted a study over bile acids. Bile acids are synthesized from cholesterol in the liver,[20] stored in the gallbladder and discharged through the common bile duct into the duodenum; 95% of the bile acids are reabsorbed back into the blood at the end of the ileum. In the colon, CDCA and LCA activate TGR5 receptors on enteric neurons to stimulate the intestine, increasing intestinal mucosal permeability and peristalsis, thus affecting the consistency of stool. Bile acid is closely

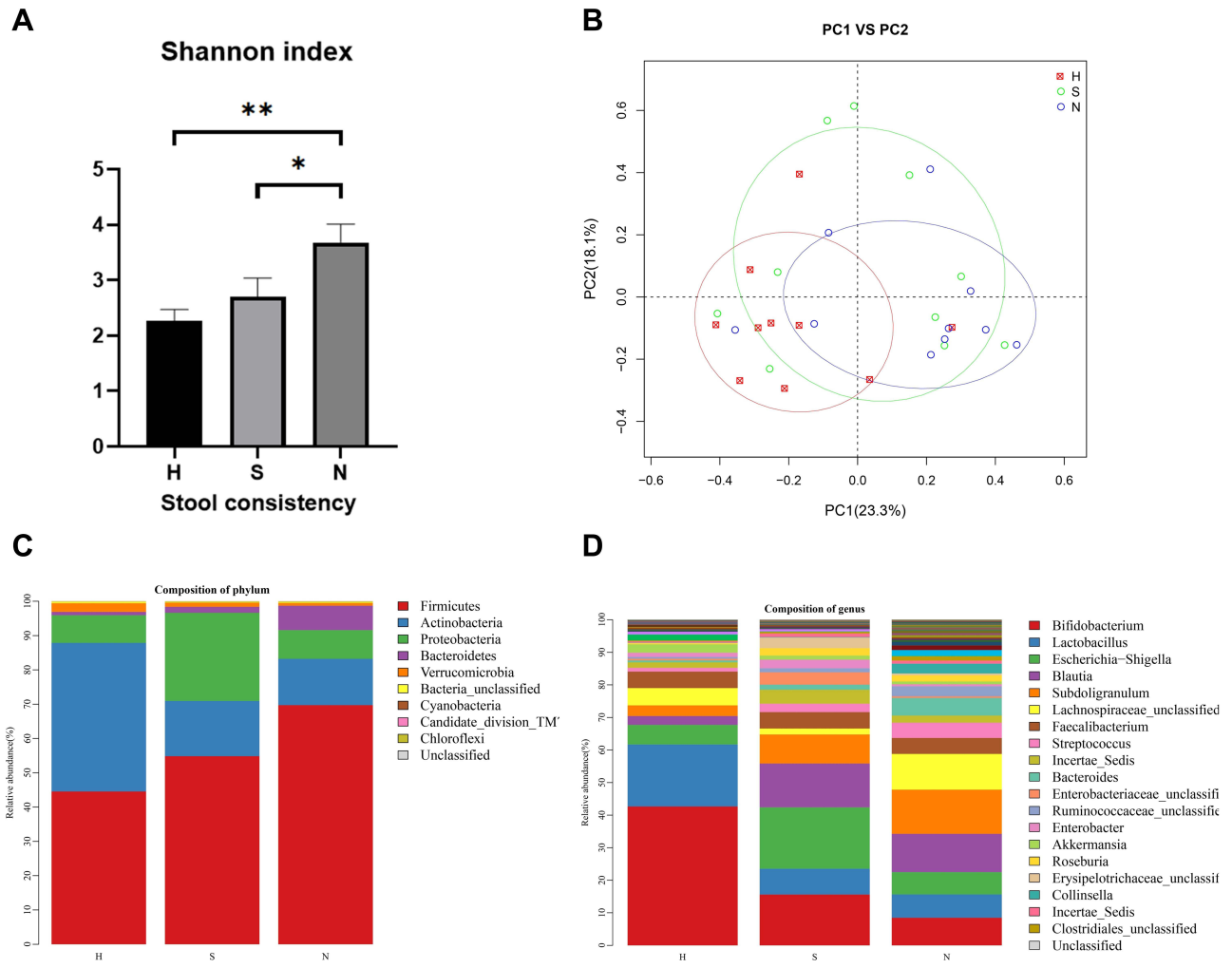

Figure 3 Classification of microbial diversity in patients with different fecal consistencies. (**A**) The Shannon index of group N was significantly higher than that of Group H and Group S. (**B**) These three groups were separated into different clusters in the UniFrac PCoA. (**C** and **D**) Bar plots of the relative abundances of the three groups at the phylum level and the genus level. *$P < 0.05$, **$P < 0.01$.

related to diarrhea,[21] and it can also affect constipation.[22] Subjects with soft stool excretion had high levels of primary bile acids (especially CDCA), while those with hard stool excretion had high levels of secondary bile acids (especially LCA).[17]

We found that there was a significant difference between Group H and Group S concerning the proportion of bile acids in CA, CDCA, and LCA. The proportion of bile acids of Group N was in the middle of the Group H and Group S and had no significant difference from that of Group S. Only LCA was significantly different between Group N and Group H. Too many or too few bile acids often have similar effects. For example, too much LCA can inhibit the growth of *Clostridioides difficile* (*Clostridioides difficile* is related to weight loss and the improvement of glucose tolerance)[23] and aggravate T2DM, while too little LCA fails to inhibit the growth of *E. coli*, tends to induce intestinal inflammation,[24] and also can aggravate T2DM. In addition, DCA also has the dual effects of aggravating and mitigating intestinal inflammation.[25,26]

Multiple regression showed that ImP was positively correlated with TCA in feces. TCA is an important factor affecting energy metabolism[27] and intestinal flora, and plays an important role in the development of intestinal flora.[28] TCA is also a great booster for the growth of *Giardia Lamblia*, which can cause diarrhea.[29] ImP was negatively correlated with GCA in blood. This may be because GCA is positively correlated with body weight and decreases with weight loss,[30] while ImP is negatively correlated with body weight (P =0.175). Despite a limited number of patients

under study, previous studies established that ImP levels in obese T2DM subjects were lower than those in normal T2DM subjects, which was consistent with our findings. Low levels of ImP favor metformin in its potency, which is consistent with metformin's efficacy in treating Type 2 diabetes with obesity.[31] However, the relationship between ImP and obesity still needs further investigation.

The Shannon index of Group N was significantly higher than that of Group H and S, suggesting that the change in the microbiome diversity was closely related to ImP.[32] The *Bifidobacterium* in Group H was significantly higher than that in Group N and S, which might be a result of the higher content of CDCA in the feces of Group N and S. Under normal circumstances, CDCA changes from microbiome dehydroxylation to LCA, and an increase in CDCA indicates rapid peristalsis of the colon or insufficient dehydroxylation time due to changes in the microbiome, which leads to the reduction of *Bifidobacterium*. Although *Bifidobacterium* has been regarded as a beneficial bacterium, studies have indeed shown a positive correlation between *Bifidobacterium* and abdominal pain, discomfort and bloating.[33]

ImP is related to diet, especially the intake of high protein foods such as cheese, milk or eggs.[10] A high-protein diet can reduce HbA1c levels in T2DM patients but increase the frequency of gastrointestinal symptoms such as diarrhea and constipation with abnormal stool consistency.[34] According to our study, abnormal stool consistency can increase ImP, which explains why ImP is positively correlated with the intake of cheese, milk and eggs.

ImP can reduce the curative effect of metformin, and our study has shown that abnormal stool consistency can lead to an increase in ImP. The main side effects brought about by metformin include diarrhea, abdominal distension, nausea, constipation and other gastrointestinal symptoms with abnormal stool consistency. That is to say, after the intake of metformin by T2DM patients, the side effects arising from abnormal stool consistency will probably lead to an increase in ImP, thus reducing the curative effect of metformin. Supplementation of short-chain fatty acids can reduce the side effects of metformin and therefore, improve its curative effect,[3] which is consistent with our guess. It suggests that treating gastrointestinal symptoms may be one of the approaches to improving the efficacy of metformin.

Our study has a few limitations. First, the sample size was small, with only 96 T2DM subjects and 45 healthy subjects; and the sample coverage is limited, as only Chinese participants were included. Second, there are more than 50 kinds of bile acids, but we only detected 13 kinds of typical bile acids. It is possible that some bile acids excluded from our detection are low in content, but they have a great influence on the stool consistency. Moreover, human feces can only reflect the changes in the content of bile acids in the colon, mainly the secondary bile acids (DCA and LCA) generated by the metabolism of intestinal flora, and nearly 95% of the bile acids are reabsorbed into the blood in the ileum. The content of these bile acids is not clear, and it cannot reflect the changes in the bile acids excreted by the liver and the small intestine. Stool consistency is also subject to many other factors, such as intestinal nerves, intestinal permeability and so on. Due to limited conditions, those factors were not included in our analysis.

Conclusions

The present study has clearly shown the relationship between the ImP level and the stool consistency, which has to do with the proportion of bile acids and changes in the fecal microbial structure. These findings may help improve the treatment of T2DM by improving the stool consistency.

Abbreviations

ImP, imidazole propionate; T2DM, type 2 diabetes; TC, total cholesterol; BMI, body mass index; HDL, high-density lipoprotein cholesterol; TG, triglycerides; LDL, low-density lipoprotein cholesterol; CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; LCA, lithocholic acid; TUDCA, tauroursodeoxycholic acid; HDCA, hyodeoxycholic acid; GUDCA, glycoursodeoxycholic acid; GDCA, glycodeoxycholic acid; TDCA, taurodeoxycholate; UDCA, ursodeoxycholic acid; GCDCA, glycochenodeoxycholate; GCA, glycocholic acid; TCA, taurocholic acid.

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Disclosure

The authors report no conflicts of interest in this work.

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