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Study on gut microbiota and metabolomics in postmenopausal women

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Abstract

Menopausal syndrome, occurring during the menopausal stage in women, manifests as symptoms stemming from decreased estrogen levels, such as hot flashes, insomnia, mental disorders (anxiety, depression), and osteoporosis. The bulk of studies have indicated alterations in the gut microbiota of those experiencing menopause syndrome compared to healthy women. However, This article focuses on the alterations in gut microbiota in perimenopausal women. Our study utilized 16 s rRNA sequencing to determine the differences in the gut microbiota and metabolites among 44 menopausal syndrome women. The distribution of gut microbiota in postmenopausal women varies based on the level of follicle stimulating hormone, with changes in gut microbiota abundance taking precedence over symptom onset. Fecal metabolites reveal changes in several metabolites, including Amino acid metabolism (Tyrosine, Tryptophan), Lipid metabolism (Alpha linolenic acid metabolism), and other metabolites. Disturbances in lipid metabolism, triggered by hormonal level fluctuations, can contribute to the development of osteoporosis.

Keywords 16 s rRNA, Gut microbiota, Fecal metabolites, Perimenopausal syndrome

Introduction

Perimenopause represents a transitional phase in middle age that precipitates reproductive aging in women [1–4], constituting a natural facet of the aging process and a physiological milestone in women's lives [5]. The initial indication of menopause may manifest through menopausal symptoms, stemming from a decline in ovarian estrogen secretion [6]. These symptoms encompass a wide array, such as dizziness, arrhythmia, atrophic vaginitis, bladder irritability, emotional fluctuations, sleep disorders, headaches, muscle and pain, difficulty concentrating, memory loss, and more. Among them, the most prevalent are vasoconstriction symptoms, commonly referred to as hot flashes (HF), and night sweats [7, 8]. In addition, reduced estrogen levels during menopause can bring about systemic alterations, including bone loss, increased abdominal fat, and heightened cardiovascular risk [9]. Certainly, not all women experience overt symptoms. The endocrine characteristics of postmenopausal women typically includes elevated secretion of gonadotropins (Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH)), sustained low levels of ovarian steroids (Estradiol, Progesterone), and comparatively diminished levels of testosterone secretion [10]. he menopausal transition period and perimenopausal period mark the transitional stages from reproductive to non-reproductive life [11]. However, they can significantly disrupt women's daily routines, prompting them to seek medical assistance. For certain individuals, these symptoms may profoundly diminish their quality of life.

The gut microbiota denotes the typical microbial community inhabiting the human body. Then, the human microbial community means genomic assemble together

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microorganisms residing within the human body, comprising bacteria, bacteriophages, fungi, protozoa, and viruses [12]. As well as, the categories of human genes include the human genome and the human microbiome, with the human symbiotic microbiome being acknowledged as the "second human genome". Microorganisms have been implicated as the instigators of many disease mutations and possess the capability to influence host phenotypes[13]. A burgeoning body of research suggests a profound correlation between gut microbiota and both health and disease states. The intestinal microbiota is perceived as an integral human organ, hosting a vast colonization of 1013–1014 bacteria within the intestine, primarily situated in the intestinal lumen and mucosal regions [14]. Concurrently, evidence suggests a noteworthy impact of gut microbiota on estrogen metabolism levels [15]. For example, dysbiosis of the gut microbiota is associated with many female reproductive endocrine diseases, such as endometriosis [10], polycystic ovary syndrome [11], oobesity, and precocious puberty [16–18]. In addition, the gut microbiota exerts influence on the host by secreting metabolites into the bloodstream. Maybe, the gut microbiota assumes a crucial role in modulating the estrogen cycle, metabolism, and the immune system.

Presently, the predominant focus of menopausal studies lies in contrasting the distinctions in gut microbiota between perimenopausal women and their healthy counterparts, with scant investigations delving into gut microbiota based on symptomatic presentations in perimenopausal women. Numerous articles indicate that FSH is closely related to bone loss, bone density, and other factors in perimenopausal women[19–22]. Hence, this study focused on 44 perimenopausal women, categorizing them into two cohorts depending on whether FSH exceeded 40. The fecal microbiota and metabolites were assessed through 16sRNA sequencing. The present study endeavors to evaluate the diversity of microbial and metabolite composition and functional changes between the two groups. The overarching objective is to offer pioneering insights and strategies for finding new treatment methods aimed at enhancing the quality of life of postmenopausal women.

Methods

Sample information

This study adopted a case–control design and divide into two groups G1 and G2, comprising a total of 44 outpatient participants for investigating the gut microbiota. Among these patients, six parameters were examined. Participants were segregated into two groups based on FSH levels. An FSH level below 40 denoted a decline in ovarian reserve function (G1, $n=16$), while a level exceeding 40 indicated premature ovarian failure (G2, $n=28$). This study had obtained approval from the Medical Ethics Committee (Approval Number: NOY [2021] 16).

Diagnostic criteria for perimenopause

The main diagnostic criterion for perimenopause revolves around estrogen levels. According to clinical guidelines in obstetrics and gynecology, accompanying symptoms include menstrual disorders, hot flashes, osteoporosis resulting from calcium loss, and various mental disturbances such as depression, insomnia, anxiety. The severity of symptoms during the perimenopausal period fluctuates according to the K-score [23].

Data collection

Patients were provided with fecal collection tools. Following the collection of fecal samples, the specimens were stored at -80 ℃ for subsequent 16S rRNA sequencing and metabolome analysis. Furthermore, 3 ml of venous blood sample were collected from patients,then separate the serum and use a fully automatic chemiluminescence detector and its supporting reagents to assess six reproductive hormone parameters[24].

Sample DNA extraction, PCR amplification, and sequencing

Total genomic DNA was extracted from samples using the TGuide S96 Magnetic Soil / Stool DNA Kit (TianGen Biotech (Beijing) Co., Ltd.), following the manufacturer's instructions. PCR products were subsequently checked on agarose gel and purified using the Omega DNA purification kit (Omega Inc., Norcross, GA, USA). The purified PCR products were then collected, and paired-end sequencing (2×250 bp) was performed on the Illumina Novaseq 6000 platform. Adjustments to the primer were made as necessary to align with the actual amplification subregion.

Metabolome analysis

The LC/MS system utilized for metabolomics analysis comprised the Waters Acquity I-Class PLUS ultra-high performance liquid tandem Waters Xevo G2-XS QTof high resolution mass spectrometer. The column employed was procured from Waters Acquity UPLC HSS T3 column (1.8um 2.1*100 mm). Following sample processing procedures including extraction and centrifugation, the raw data acquired via MassLynx V4.2 was subjected to data processing operations using Progenesis QI software for tasks such as peak extraction, peak alignment, and other. Identification is facilitated through the Progenesis QI software online METLIN database and Biomark's self-built library. Concurrently, theoretical fragment identification and mass deviation were maintained within 100 ppm. Subsequent analysis is conducted

following normalization of the original peak area information with the total peak area.

Data analysis

A diversity was analysed to identify the complexity of species diversity within each sample utilizing QIIME2 software. β diversity was calculated through principal component analysis (PCA) gauge the diversity across samples for species complexity. One-way analysis of variance was employed to compare bacterial abundance and diversity. T-tests were performed on species abundance data between groups using Metastats software [25]; and *p*-values were obtained and corrected to *q*-values. Subsequently, species causing differences in sample composition between the two groups were selected based on the obtained *p*-value or *q*-value. Principal component analysis and Spearman correlation analysis were employed to assess the repeatability of the samples within group and quality control samples. Differential metabolites were screened using a combination of difference multiples, *p*-values, and Variable Importance in Projection (VIP) values from the OPLS-DA model. The screening criteria comprised VIP values greater than 1, fold change(FC) greater than 1, and *p*-values less than 0.05. The online platform BMKCloud (https://www.biocloud.net) was utilized for analyzing the sequencing data.

Results

Inclusion criteria for clinical participants

The present study encompassed 44 perimenopausal patients, whose clinical manifestations and symptoms were documented and summarized. The severity of perimenopausal syndrome was assessed using the K-score [23], which categorizes it into four levels: normal (K-score < 6), mild (6–15), moderate (16–30), and severe (K-score > 40). As shown in Table 1, among women with FSH greater than 40, the majority of perimenopausal symptoms are moderate. But there was no significant difference in their K-scores. All patients underwent testing for six sexual indicators (FSH, LH, E2, P, T, PRL), and they were divided into two groups based on FSH levels: G1 ($n=16$) for FSH < 40 and G2 for FSH > 40 ($n=28$). We categorize the symptoms of perimenopause into three categories: hot flashes, bone pain, and mental disorders. It was observed that individuals in the G1 group predominantly experienced mental disorders, whereas those in the G2 group primarily manifested hot flashes and bone pain. Furthermore, as shown in Table 2, we performed a statistical analysis of credit that took into account the age and six hormones of the two groups. Age($P=0.052$), T ($P=0.074$), PRL($P=0.541$) or other aspects are not significantly different between the two groups, indicating that age and T, P have minimal impact on gut microbiota. however, FSH and LH in the G1 group were higher than those in the G2 group, while E2 and P were lower in the G1 group.

Analysis of gut microbial diversity and species distribution

The analysis of gut microbial diversity involved an assessment of α diversity, Chao1 and Ace indices measure species richness, the number of species present. The Shannon and Simpson indices were measured to discern species diversity, where higher values indicate greater species diversity within the sample. Results indicated no statistically significant difference in ACE index (Fig. 1a) and Shannon index (Fig. 1b) between the two groups.

Table 2 Basic characteristics

Parameters	G1 group ($n=28$)	G2 group ($n=16$)	*P* Value
age	47.55 ± 3.74	49.29 ± 3.02	0.052
FSH(IU/L)	78.5(59.73, 87.73)	14.3(6.84, 29)	$p<0.05$*
LH(IU/L)	37(32, 43.42)	11.07(5.83, 17.13)	$p<0.05$*
E2 (pmol/L)	26.45(18.40, 44.18)	208.8(85.5, 848.75)	$p<0.05$*
P(mmol/L)	0.24(0.16, 0.54)	0.59(0.34, 1.28)	$P<0.05$*
T(mmol/L)	0.36(0.10, 0.60)	0.58(0.34, 0.91)	0.074
PRL(mmol/L)	227.4(167, 288)	206(166.70, 267.50)	0.541

For parameters with a normal distribution, the mean is represented by ± SD, and the *p*-value were calculated using a student t-test; For non normally distributed parameters, the median were represented by IQR (P25, P75), and the *p*-value is calculated using Mann Whitney U test

FSH Follicle Stimulating Hormone, *LH* Luteinizing Hormone, *E2* Estradiol, *P* Progesterone, *T* Testosterone, *PRL* Prolactin

Table 1 The proportion of symptoms and K-score levels in each group

group	symptom				K-score		
	hot flash	osteodynia	Mental disorders (Insomnia, anxiety, depression)	Others	mild	moderate	severe
G1 group	2	4	9	1	4	9	3
(FSH < 40,$n=16$)	(12.5%)	(25%)	(56.3%)	(6.3%)	(25%)	(56.3%)	(18.8%)
G2 group	9	9	8	2	6	20	2
(FSH > 40,$n=28$)	(32.1%)	(32.1%)	(28.6%)	(7.10%)	(21.4%)	(71.4%)	(7.10%)

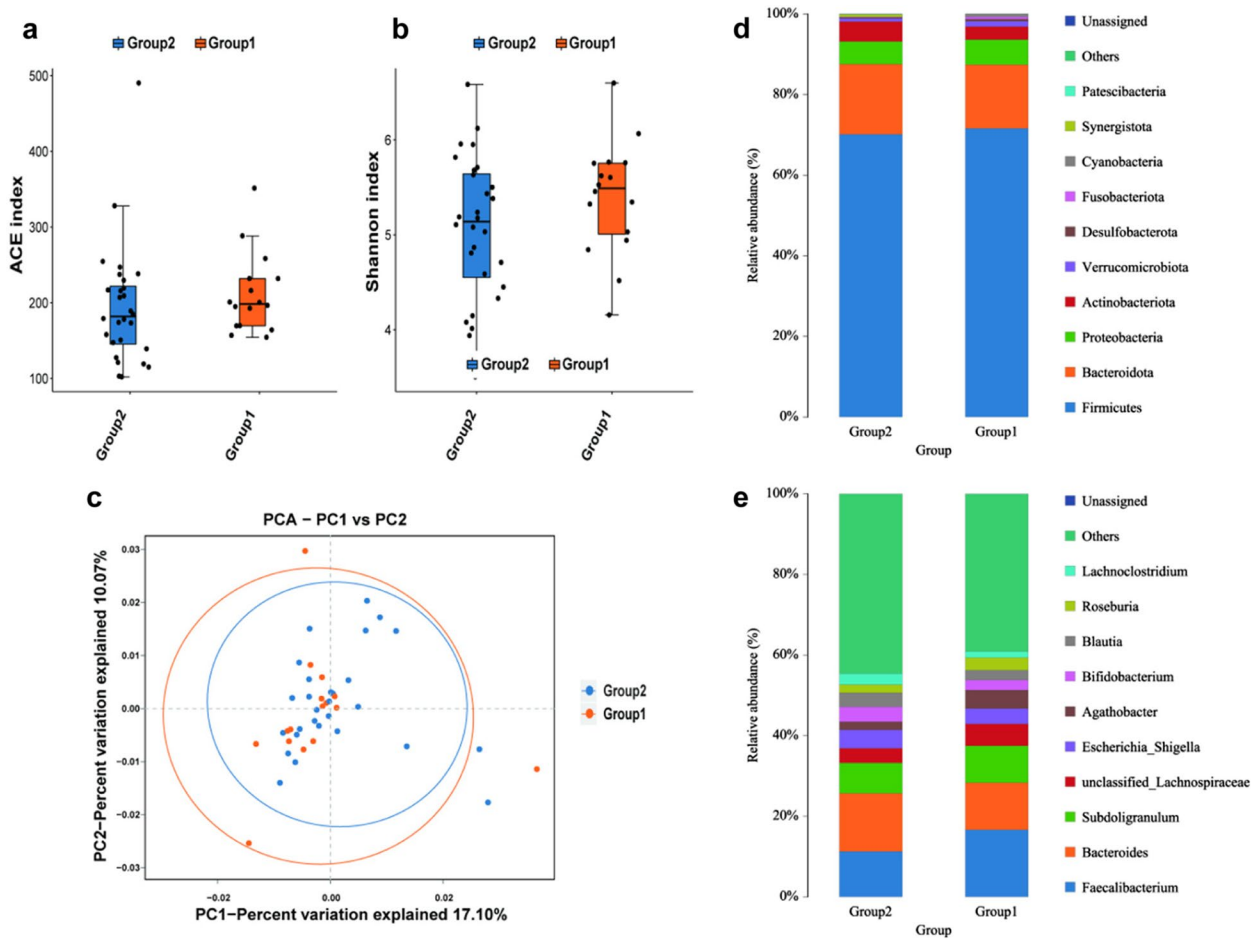

Fig. 1 Diversity analysis and species distribution of gut microbiota. **a** α Diversity analysis ACE index. **b** α Diversity analysis Shannon index. **c** Principal component analysis. **d** Distribution of species at the phylum level. **e** Distribution of species at the level of genus

In addition, β diversity between the two groups was also computed, with PCA(Fig. 1c) revealing no statistically significant difference.

An analysis was conducted on the species distribution within two groups of samples at the phylum and genus levels of bacteria. This examination had unveiled the top 10 species present at both phylum and genus levels. At the phylum level (Fig. 1d), Verrucomimicrobiota, Fusobacteriota, Cyanobacteria, Desulfobacteriota, protobacteria, Firmicutes within G1 surpassed those within G2 in abundance; Synergistota, Bacteroidota, Actinobacteriota exhibited greater prevalence in G2 compared to G1. At the genus level (Fig. 1e), Faecalibacterium, Subdolibranulum, Agathobacter, unclassified Lachnospiraceae, Roseburia within Group 1 exhibited higher abundance relative to Group 2; conversely, Bacteroides, Escherichia Schigella, Bifidobacterium, Blautia were more abundant in G2 compared to G1 (see Supplemental Table 1, Supplemental Table 2).

Analysis of differences in microbial community richness

In the Metastats analysis, notable distinctions in microbial community richness were observed at the taxonomic levels of phyla, class, order, family, genus, etc. At the phylum level, significant differences emerged in the communities of Bdellovibrionota and Planctomycota. Despite the absence of noteworthy disparities in the richness of Actinobacteriota and Desuifobacterota, they ranked among the top ten microorganisms in terms of species distribution. At the genus level, significant differences were identified among the top ten microbial communities in terms of richness, with unclassified lachnospiraceae bacteria also ranking among the top ten microorganisms in species distribution. This highlighted a significant divergence in the composition of gut microbiota between the two groups in comparison to microorganisms Fig. 2.

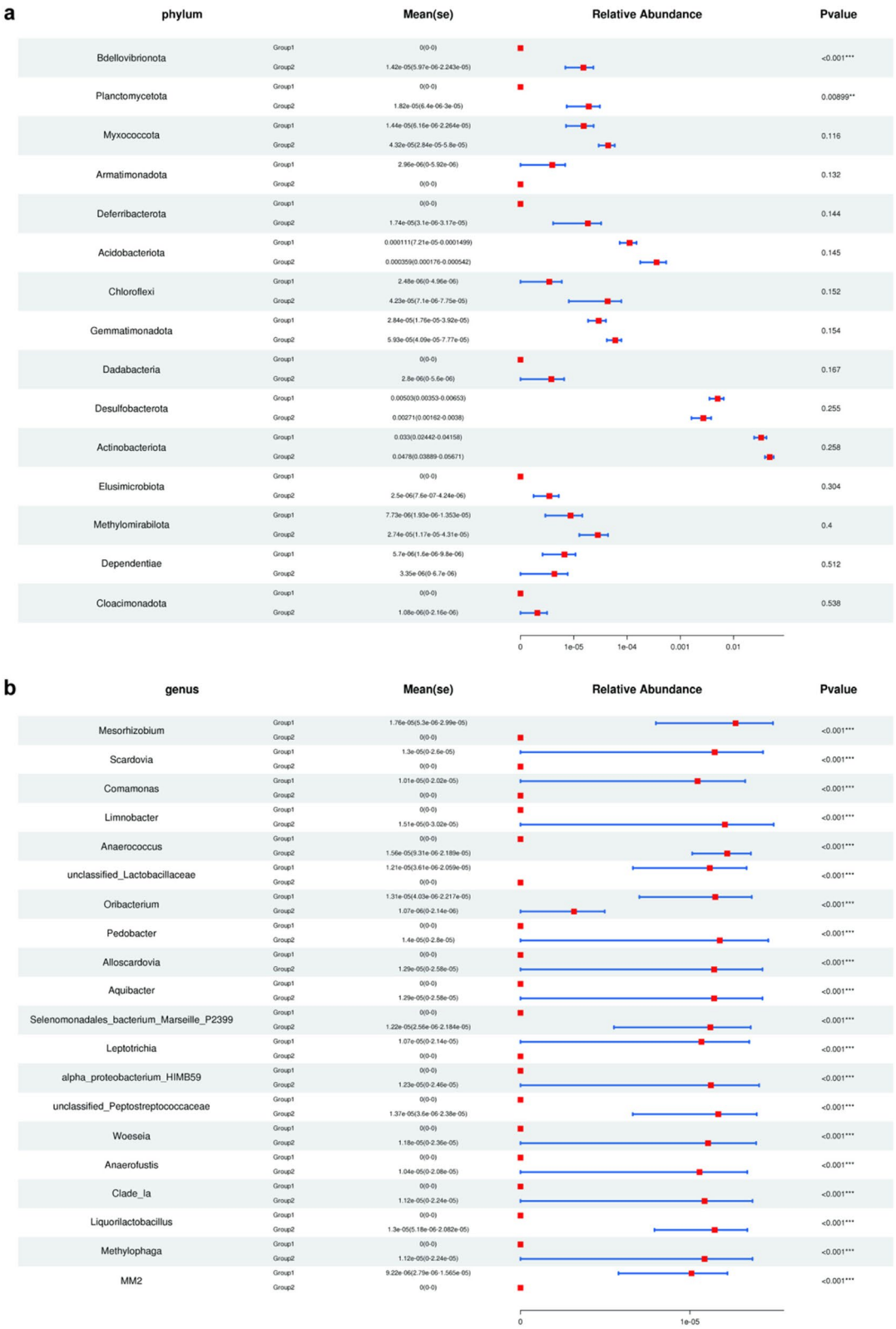

Fig. 2 Metastats analysis statistical chart. **a** phylum level. **b** genus level

The correlation between clinical parameters and gut microbiota

Spearman analysis was used to explore the correlation between clinical parameters and species richness at the genus level. As shown in Fig. 3, the results revealed that FSH exhibited a negative correlation with *Subdoligranum*, *Agathobacter*, and *UCG_002*; meanwhile, Luteinizing Hormone(LH) displayed a negative correlation with *Subdiligranulum*. Conversely, Prolactin(PRL) demonstrated a positive correlation with *Ruminooccus*, while Progesterone(P) exhibited a positive correlation with *Monologues* and the most pronounced negative correlation with *Megamonas*. Moreover, Estradiol(E2) showed a positive correlation with *Monologues*, *Facalibaterium*, *Dialister*, and *unclassified Lachnospiraceae*.

Metabolomics analysis of fecal metabolites in perimenopausal patients

To further evaluate the relationship between metabolites and perimenopausal syndrome, we used PLUS ultra-high performance liquid chromatography in series with Waters Xevo G2-XS QTOF high-resolution mass spectrometer to evaluate the fecal metabolites. Prior to conducting differential analysis of metabolites, PCA was performed on each differential metabolite group to assess the variance between the distinct groups and within-group samples. As depicted in Fig. 4a, PCA results indicated a high degree of similarity between the two groups, with no significant differences observed. Subsequently, a differential abundance metabolite analysis was conducted, leading to the identification of a total of 6831 metabolites, among which 50 were deemed differential. Of these, 46 differential metabolites were upregulated while 4 differential metabolites were downregulated, as illustrated in Fig. 4b, in which highlighted the significantly different metabolites. Furthermore, we explored potential pathways related to differentially enriched metabolites through KEGG pathway analysis. As shown in Fig. 4c, the metabolic pathways of menopausal patients predominantly encompassed amino acid metabolism, digestive system, biosynthesis of other secondary metabolites, carbohydrate metabolism, lipid metabolism, and

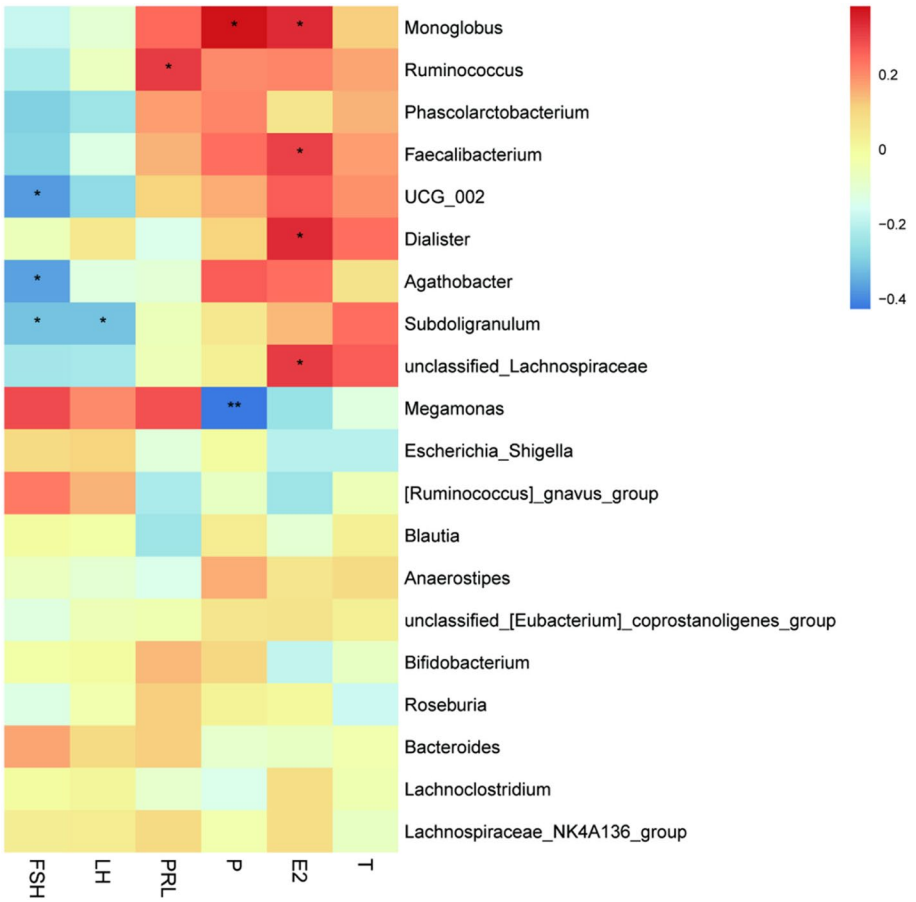

Fig. 3 The relationship between clinical parameters and microorganisms, with red indicating positive correlation and blue indicating negative correlation. (FSH: Follicle Stimulating Hormone, LH: Luteinizing Hormone, PRL: Prolactin, P: Progesterone, E2: Estradiol, T: Testosterone)

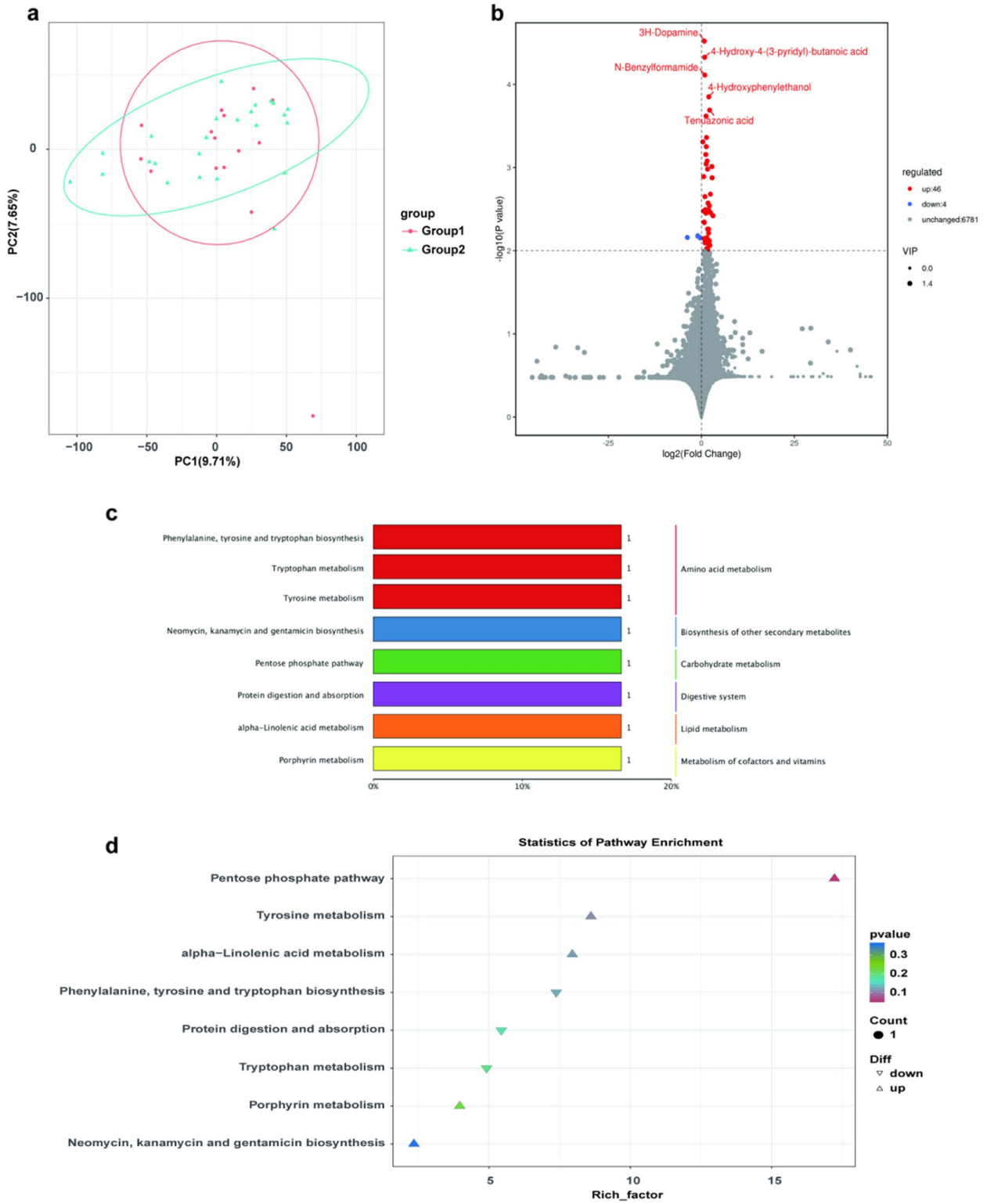

Fig. 4 Differential metabolite analysis. **a** Principal component analysis chart. **b** Differential metabolite volcano map. **c** Classification diagram of differential metabolite pathways (The different colored entries in the figure represent the hierarchical classification annotations of the KEGG pathway, corresponding to KO pathway level 2 and KEGG pathway names. The length of the column represents the number of differential metabolites annotated by this pathway). **d** KEGG enrichment map of differential metabolites (The color depth of the dots represents the *P* value, the smaller the *P* value, the more reliable the enrichment significance of differential metabolites in this pathway. The upper triangle indicates that differential metabolites in the pathway are upregulated, and the lower triangle indicates the opposite)

metabolism of cofactors and vitamins. As depicted in Fig. 4d, the enriched upregulated metabolites included tyrosine metabolism, neomycin, kanamycin, and gentamicin biosynthesis, pentose photoschate pathway, and alpha linolenic acid metabolism, and porohyrin metabolism. Conversely, the enriched down regulated metabolites encompassed phenylalanine, tyrosine and tryptophan biosynthesis, tryptophan metabolism, protein digestion and absorption.

Correlation analysis between changes in gut microbiota and fecal metabolites in perimenopausal patients

We examined the alterations in microbial composition of perimenopausal patients in relation to microbial metabolites, and Spearman correlation molecules showed several significant correlations between their gut bacteria and metabolites (Fig. 5). Stercobilin (fecal bile pigment) was positively correlated with [Eubacteria]_eligens_group, UCG:009, and unclassified DTL014, while displaying a negative correlation with Anaerotruncus. D-Sedoheptulose 7-phase was negatively correlated with Phascolarium and Anaerotruncatus, and positively correlated with MM2 and Prevotellaceae UCG 001. A positive correlation was observed between Difelikefalin and UCG-009, Lachnospiraceae_FC5020_group, and Marvinbryantila. Arg-Pro-Pro-Gly-Phe-Ser-Pro exhibited a negative correlation with Anaerotruncatus and a positive correlation with Marvinbryantila. Canarigenin 3- [glucosyl—(1- > 4) -6-deoxyalloside] displayed positive correlations with Ilumatobacter, unclassified Lactobacillaceae. Tenuazonic acid was positively correlated with UCG009 and Marvinbryantila. There is a positive correlation between Chemb4238926 and unclassified DTL014, Lachnospiraceae FC5020_group, Mailhella, Prevotellaceae UCG 001. Salutaridinol demonstrated positive correlations with Ilumatobacter, unclassified Lactobacillaceae, and Mogibacterium.

Discussion

Both historical and contemporary research endeavors have delineated a discernible correlation between estrogen levels and gut microbiota [26, 27], underscoring the

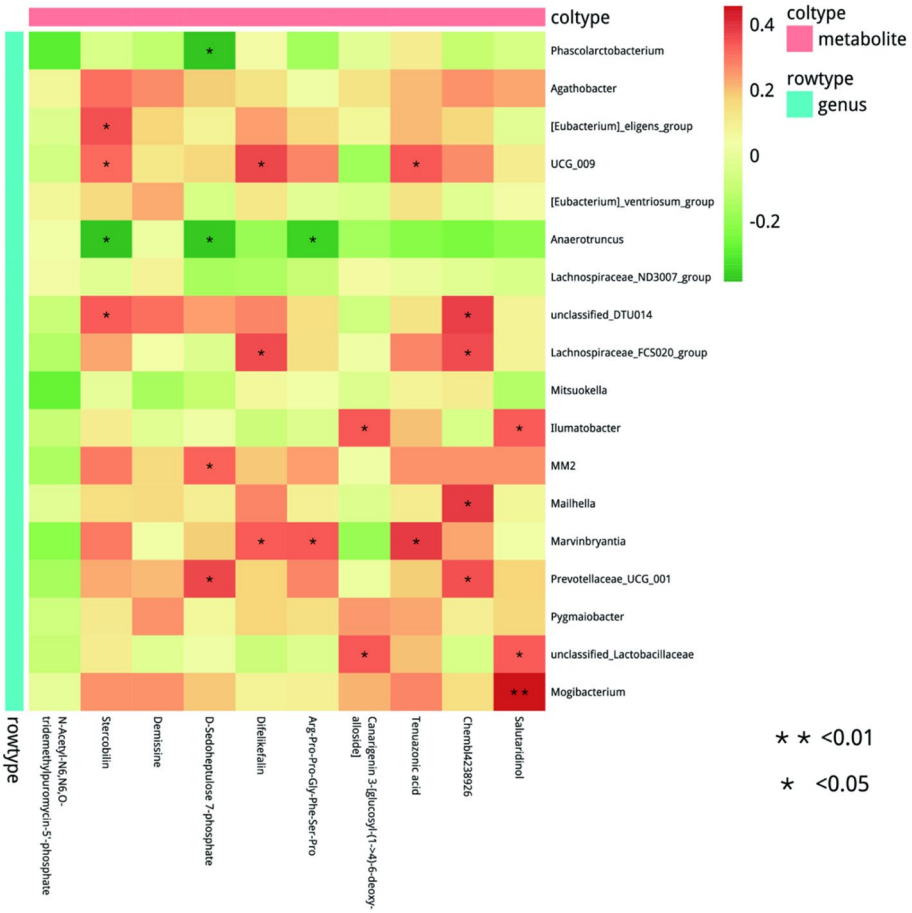

Fig. 5 The relationship between gut microbiota and gut metabolism, with red and yellow indicating positive correlation and green indicating negative correlation. The significance of the chart is represented as follows: $P < 0.01$ **, $P < 0.5$*

consequential impact of estrogen levels on microbial dynamics. Throughout the menopausal stage in women, diminishing ovarian function precipitates a reduction in estrogen production by the ovaries, concomitantly leading to elevated FSH levels in in circulation. Certain female hormones and estrogen, including FSH, exert pivotal regulatory influence over the composition of intestinal microbiota [28, 29]. In clinical practice, estrogen levels manifest fluctuating patterns, with FSH emerging as a more sensitive diagnostic marker within the age bracket of 45–55 years. Notably, our investigations unveiled that FSH upon surpassing a threshold of 40, indicative of declining ovarian function in females, the manifestations associated with the perimenopausal phase exhibited exacerbation. The majority of patients had moderate K scores, with bone pain and hot flashes being the main symptoms.

Osteoporosis and decreased bone mass represent prevalent metabolic bone diseases in postmenopausal women [30]. he composition of gut microbiota is intricately linked to the bone structure of postmenopausal women. Studies have reported an increase in gut permeability during the perimenopausal period, which is related to the decrease in bone density [31]. Moreover, based on FSH categorization, bone pain emerges as a predominant symptom among perimenopausal women with FSH levels surpassing 40. Multiple studies [32, 33] have compared the gut microbiota of postmenopausal women with osteoporosis to those with normal bone mass, revealing significant disparities in their gut microbiota composition. In one such study [33], perimenopausal women with a diminished abundance of Bacteroidete demonstrated a significantly elevated fracture rate compared to their control counterparts. Additionally, another study reported a higher prevalence of Bacteroidete in individuals with osteoporosis [30]. The impact of Bacteroidete on osteoporosis may stem from its role as the main synthetic bacterium of vitamin K, which has been implicated in the prevention or treatment of osteoporosis by enhancing bone mineral density [34]. In the current study, the abundance of Bacteroidetes in the G2 group was higher than that in the G1 group, with the proportion of individuals experiencing bone pain being correspondingly higher in the G2 group.

Bifidobacterium, recognized as a psychobiotic, may exert a preventive role against depression- or anxiety-like behaviors when consumed in adequate quantities [35]. Evidence from various sources[36, 37] suggests that both healthy individuals and patients with schizophrenia who consume probiotic supplements containing bifidobacteria exhibit reduced levels of depression and anxiety. Furthermore, both animal and human studies [36, 38, 39] have provided compelling evidence of the substantial efficacy of probiotic intervention with bifidobacteria in alleviating symptoms in individuals with severe depression. In our study cohort of women experiencing menopausal syndrome, Bifidobacterium was detected, with higher abundance noted in the G2 group. Remarkably, analysis of clinical data revealed a lower incidence of mental symptoms in the G2 group compared to the G1 group. Our findings provide further support for the notion that Bifidobacterium exerts a discernible impact on mental disorders such as depression.

Previous reports have highlighted changes in gut microbiota occurred during the perimenopausal period, also referred to as the premenopausal phase [40]. In our study, variations in gut microbiota and metabolites were observed among perimenopausal women, which were related to changes in estrogen levels. This association may stem from the influence of female hormones, such as estrogen, on the microbiota across various body compartments, particularly within the intestines [41]. Although no significant variance in microbial composition diversity was observed in our study, notable discrepancies were evident in the distribution of microorganisms and metabolites. Specifically, Firmicutes and Roseburia were found to be higher in the G1 group compared to the G2 group, with clinical data indicating a higher prevalence of mental disorders in the G1 group relative to the G2 group. In addition, estrogen has been demonstrated to impact the gut microbiome, with multiple studies reporting significant differences in gut microbiota and metabolites between premenopausal and postmenopausal women [41, 42]. On the other hand, a decline in estrogen can lead to many other menopausal symptoms [43], such as vasospasm (hot flashes), sleep disorders and insomnia, and negative affective states such as anxiety and depression. Both human and animal studies have underscored the relationship between negative emotions and the composition of gut microbiota [40, 44, 45]. Previous investigations have noted a significant decrease in microbial richness and diversity in patients or mice with anxiety disorder [45]. At the phylum level, individuals or mice with anxiety disorders typically exhibit lower levels of Firmicutes [45]. Furthermore, a study [42] reported a reduction in the abundance of Firmicutes and Roseburia spp. in the feces of postmenopausal women.

Blautia, as a symbiotic genus of specialized anaerobic bacteria, assumes a pivotal role in preserving intestinal ecological equilibrium and mitigating inflammation by upregulating intestinal regulatory T cells and synthesizing short chain fatty acids [46]. Faecalibacterium, renowned for its production of butyric acid, exerts anti-inflammatory properties, sustains the activity of bacterial enzymes, and safeguards the digestive system from intestinal pathogens [47]. Reduced levels of

Faecalibacterium have been documented in individuals afflicted with chronic constipation, celiac disease, irritable bowel syndrome, and inflammatory bowel disease (including Crohn's disease and ulcerative colitis) [48]. In this study, compared to the G1 group, the G2 group showed an increase in Blautia abundance and a decrease in Faecalibacterium abundance, with Faecalibacterium demonstrating a positive correlation with E2. In the context of perimenopausal insomnia (PI), our studies have documented an augmentation in Blautia abundance alongside a reduction in Faecalibacterium abundance [49]. This characteristic may be related to the reduction of anti-inflammatory butyrate bacteria. However, the precise mechanism underlying the roles of Blautia and Faecalibacterium in perimenopausal women remains elusive. Nonetheless, their abundance profiles hold promise as potential diagnostic or therapeutic targets for related conditions.

We also scrutinized the fecal metabolites of perimenopausal patients, revealing an enrichment of lipid metabolite, particularly alpha linolenic acid metabolism, in postmenopausal women. Multiple studies [50–52] have shown that lipid metabolism disorders are closely related to postmenopausal osteoporosis. The cessation of ovarian function leads to osteoporosis [53]. Through the establishment of a mouse bilateral ovariectomy model, a previous study demonstrated that alterations in hormone levels induce metabolic disorders, especially lipid metabolism disorders, which are intricately linked to bone density and bone resorption [51]. Comparative analysis of fecal metabolites between postmenopausal osteoporosis (PMO) patients and non-PMO individuals unveiled significant alterations in metabolites such as levulinic acid, N-acetylneuraminic acid, and their corresponding signaling pathways, notably Alpha linolenic acid metabolism and selenocompound metabolism [52] These findings offer a novel theoretical framework for the development of complementary treatment strategies for menopausal syndrome.

To sum up, altering the gut microbiota in perimenopausal patients may hold therapeutic promise for alleviating their symptoms. Currently, a large number of studies have shown that compared with the gut microbiota of premenopausal women, the gut microbiota of perimenopausal women has changed. Yet our main goal is to study the gut microbiota changes among perimenopausal women and see if they can provide new therapeutic value for clinical practice. Surely, it is important to acknowledge that this study is subject to several limitations. Firstly, the sample size is constrained. Secondly, further research is warranted to determine the feasibility and safety of fecal transplantation as a preventative measure for potential risks in perimenopausal women. Lastly, additional longitudinal cohort studies and animal experiments are imperative to validate our findings. Investigation into the gut microbiota of perimenopausal women not only fosters novel insights into disease pathogenesis but also presents avenues for tailored therapeutic interventions.

Conclusion

The current study assessed disparities in the distribution of gut microbiota and the composition of metabolites among perimenopausal women. Based on our research findings, we propose a hypothesis that the severity of the menopausal symptoms is affected by FSH and gut microbiota. The connection between FSH and osteodynia in women was further explored, women in the G2 group (FSH > 40) have a higher rate of experiencing bone pain symptoms. The viewpoint we have established through our microbiological research and metabolism has been confirmed. The study of intestinal microbes revealed that Bacteroides is associated with perimenopausal bone pain, and the G2 group had a higher incidence rate of Bacteroides. As well as, our study of metabolites show that postmenopausal osteoporosis is a result of odysregulation of lipid metabolism. However,due to the limited sample size, our findings did not yield significant differences in symptoms between the two groups. But certain bacteria showed suggestive associations with symptom manifestation, offering potential insights for clinical treatment strategies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12905-024-03448-7.

Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions

This project was conceived and designed by X.Y.X and Y.W.L. The project was managed by Y.W.L and S.L. Clinical diagnosis was performed by M.L and Y.W were in charge of collecting the samples and administering the questionnaires to the participants. J.B.S and W.F.G contributed to metagenomic data analysis. The manuscript was written by X.Y.X. The manuscript was drafted with the help of J.B.S, M.L, Y.W W.F.G, S.L and Y.W.L. The final version of the manuscript was approved by all authors.

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Data availability
The data produce in this study can be traced in the NCBI database with accession code SRA: PRJNA1182052.

Declarations

Ethics approval and consent to participate
This study was approved by the ethics committee review board of the Guangzhou University of Traditional Chinese Medicine Affiliated Gaozhou Traditional Chinese Medicine Hospital (Approval No.NOY (2021) 16). All participants are informed and have signed an informed consent form.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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