Gut Microbiota Feature of Senile Osteoporosis

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Senile osteoporosis is defined as an age-related bone metabolic disorder, which is characterized by bone loss and decreased bone fragility. Gut microbiota (GM) could regulate the bone metabolic process and be closely related to senile osteoporosis. Several genus-level GM were found to increase in osteoporotic animals and patients. However, to reveal the pathogenic bacteria in senile osteoporosis, further studies are still needed to investigate the complete characteristics of bacteria species. GM are defined as the collection of commensal bacteria living in the digestive tract, which regulates host metabolism and performs various functions. GM of humans consist of over 1000 distinct bacterial species, about two-thirds of which are unique to each individual. GM have an impact on many chronic diseases, such as obesity, diabetes, neurological disorders, inflammatory bowel disease (IBD), and cardiovascular disease. As a member of the chronic disease category, osteoporosis is also associated with GM.

senile osteoporosis gut microbiota bacteria species shallow shotgun functional metabolic pathway

1. Introduction

Senile osteoporosis is a primary, age-related bone metabolic disease, which is characterized by bone loss and decreased bone fragility[1]. Commonly, primary osteoporosis mainly affects postmenopausal females and aged males. Commonly, postmenopausal females have a higher incidence of fragility fractures, while aged people, especially aged males, have a higher rate of mortality related to osteoporosis[2]. Emerging evidence demonstrated that aging plays a critical role in the development of osteoporosis[3]. With the gradual rise of an aging population, senile osteoporosis has brought a higher burden on the public health system[4].

Recent studies suggested that senile osteoporosis was closely related to gut microbiota (GM). Several clinical studies reported that the osteoporotic patients showed altered GM, richness, diversity, relative GM abundance, and functional metabolic pathways[5][6][7][8][9]. However, due to the distinct geographical location, sample size, gender distribution, and dietary habits of patients, these clinical studies have not reached a consistent conclusion on the regulation of GM alteration in osteoporotic people. In an animal study, senile osteoporotic rats showed decreased α diversity, altered β diversity, and increased relative abundance of *Helicobacter*, *Rothia*, *Clostridium IV, Alistipes,* and *H. rodentium* using 16S rRNA, and the whole metagenome sequencing (WMS)[10]. Furthermore, another study found that GM derived from feces of aged rats led to bone loss, and increased the genus-level relative abundance of *Romboutsia, Faecalibacterium*, and *Lachnospiraceae_incertae_sedis* in young rats[11]. On the contrary, GM derived from young rats could restore the bone mass of senile osteoporotic rats and decrease the genus-level

relative abundance of *Helicobacter* and *Prevotella*[12]. GM features at the genus level of senile osteoporosis were revealed by 16S rRNA sequencing using rats model.

Shallow shotgun sequencing is a high-accuracy microbiological technology, which could annotate the microbial taxonomy to the species level [13][14]. In addition, it could reach nearly the same sequencing depth and accuracy as WMS technology with fewer data[15]. To date, studies based on 16S rRNA sequencing about GM and senile osteoporosis only revealed genus-level GM taxonomic features. Although some GM strains such as *H. rodentium* were found to increase in the osteoporotic rats[10], the complete species-level characteristics of GM were still unknown.

2. Current Insights

Using shallow shotgun sequencing technology, the researchers found that the senile osteoporotic rats showed decreased species numbers, distinct β diversity, and low α diversity. Furthermore, the senile osteoporotic rats had markedly distinct GM compositions at the genus and species levels. At the genus level, *Prevotella*, *Acinetobacter,* and *Salinispora* significantly increased in osteoporotic group. At the species level, *A. baumannii*, *Lachnospiraceae bacterium M18 1*, and *P. copri* significantly increased in the osteoporotic group. In addition, KEGG functional pathways analysis found that fatty acid biosynthesis, Valine/isoleucine biosynthesis, GABA biosynthesis, and ubiquinone biosynthesis were enriched in the osteoporotic rats.

The GM structure was markedly changed between senile osteoporotic rats and young rats, which could be revealed by the distinct ecological distance in β diversity. Furthermore, the OP group had fewer unique species numbers than the control group, reflecting a decreased GM richness at the species level in the OP group. Several studies reported that disease statuses were related to decreased α diversity, such as type II diabetes and Alzheimer's disease[16][17]. In this research, though there was no significant difference, ACE and Chao indexes suggested that the senile osteoporotic rats had lower α diversity, which was consistent with the previous study[10]. These results suggested that the species-level GM structure and richness markedly changed in the senile osteoporotic rats.

The relative abundance of GM could reflect the GM composition at the different taxonomic levels. At the genus level, the proportions of *Bacteroide*, *Parabacteroides*, *Escherichia*, and *Prevotella* were higher in the osteoporotic group, while the proportions of *Corynebacterium* and *Akkermansia* were higher in the control group. The increased proportion of *Prevotella* was consistent with the previous study[12]. At the species level, the proportion of *B. coprocola*, *A. baumannii*, *P. distasonis*, and *Lachnospiraceae bacterium A4* were higher in the OP group, while *C. stationis, A. muciniphila*, and *A. indistinctus* were more abundant in the control group. To identify significantly different GM, the researchers performed LEfSe analysis and found that *Prevotella, Acinetobacter,* and *Salinispora* at the genus level and *A. baumannii*, *Lachnospiraceae bacterium M18 1*, and *P. copri* at the species level were enriched in the osteoporotic group. These results suggested that altered GM species were in accordance with the alteration of GM genus. Some GM species such as *P. copri* and *A. muciniphila* were proved to be linked to bone metabolism.

P. copri, which belongs to the *Prevotella* genus that also increased, was associated with a number of autoimmune diseases, such as colitis and rheumatoid arthritis[18][19][20]. Furthermore, *P. copri* was correlated with an increase in trimethylamine oxide (TMAO), a byproduct caused by dietary choline, which has an impact on cardiovascular disease and chronic kidney disease[21]. In addition, an increased level of TMAO has a negative correlation with the degree of bone mineral density (BMD) in osteoporosis patients[22]. In the research, *P. copri* was also found to be significantly enriched in the senile osteoporotic rats. *A. muciniphila* is a newly identified beneficial species in the phylum *Verrucomicrobia*. Previous studies reported that the abundance of *A. muciniphila* was reduced in aged humans and mice[23][24]. In an animal study, *A. muciniphila* was found to restore the bone mass of osteoporotic mice[25]. Consistently, the researchers identified that *A. muciniphila* was decreased in the senile osteoporotic rats. Therefore, the researchers suggested that the increased abundance of *P. copri* and decreased amount of *A. muciniphila* were closely related to the pathogenesis of senile osteoporosis. Furthermore, *A. baumannii,* which belongs to the *Acinetobacter genus,* is a major pathogenic factor of nosocomial infections[26]. *Salinispora* is a marine actinomycete genus that produces structurally diverse and biologically active secondary metabolites[27]. *Lachnospiraceae bacterium M18* and *Lachnospiraceae bacterium A4* belong to the Lachnospiraceae family, which could produce short-chain fatty acids and were beneficial for bone health[28]. The increase in these bacteria in aged rats could be attributed to the dysbiosis of gut microbiota. However, the association of these bacteria with the pathogenesis of senile osteoporosis needs further study.

KEGG functional pathway analysis found that metabolic pathways of fatty acid biosynthesis, Valine/isoleucine biosynthesis, GABA biosynthesis, and ubiquinone biosynthesis were enriched in the senile osteoporotic rats. Fatty acids metabolism and oxidative stress and production of ROS may impact each other and further influence bone metabolism[29]. As reported, oxidative stress was closely associated with aging[30]. Therefore, the enrichment of fatty acids biosynthesis might be related to aging-induced oxidative stress. Furthermore, GABA treatment could positively regulate osteogenic differentiation[31]. The enriched GABA biosynthesis in senile osteoporotic rats might be due to a compensatory effect after bone loss. These results suggested that fatty acid biosynthesis, Valine/isoleucine biosynthesis, GABA biosynthesis, and ubiquinone biosynthesis were related to senile osteoporosis.

3. Conclusions

The researchers first manifested the complete information of species-level GM in senile osteoporotic rats. GM was significantly altered in structure and composition in senile osteoporotic rats. *B. coprocola*, *A. baumannii*, *P. distasonis*, and *Lachnospiraceae bacterium A4* and *P. copri* were higher in the senile osteoporotic group, while *C. stationis*, *A. muciniphila*, and *A. indistinctus* were decreased. Furthermore, KEGG function analysis revealed that metabolic pathways of fatty acid biosynthesis, Valine/isoleucine biosynthesis, GABA biosynthesis, and ubiquinone biosynthesis were enriched in the senile osteoporotic rats.

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