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Research on the mechanism by which a high-fiber diet regulates the gut microbiota-bile acid metabolism axis and improves glucose metabolism

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Abstract

This study examined how a high-fiber diet affects the gut–bile-acid pathway and blood sugar control in mice with type 2 diabetes. Thirty-six male C57BL/6J mice were assigned to three groups: normal control, diabetic control, and high-fiber diet. After 12 weeks, bile acids, gene markers, and gut bacterial changes were tested. LC–MS/MS showed that total secondary bile acids increased by 62%, intestinal FXR expression dropped by 35%, and plasma FGF19 rose about two times compared with diabetic controls. Gut RNA data showed higher activity of bile-acid–related genes and more Faecalibacterium, which was strongly linked with dehydroxylation levels ($r = 0.78$, $P < 0.01$). These results show that a high-fiber diet changes bile-acid balance through gut bacteria and adjusts the FXR–FGF19 signal to support better glucose control. The findings suggest that adding dietary fiber may be a simple and safe way to improve metabolism in diabetes.

Keywords

high-fiber diet, bile acids, gut bacteria, FXR, FGF19, glucose control, type 2 diabetes

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease characterized by persistent hyperglycemia, systemic inflammation, and gut microbiota dysbiosis [1]. The gut–liver axis has gained increasing attention as a key regulator of glucose and lipid homeostasis. Specifically, gut microorganisms modify bile acid (BA) profiles, which in turn influence metabolic signaling pathways that affect glucose utilization and insulin sensitivity [2,3]. Primary BAs are synthesized in the liver and subsequently converted by microbial enzymes—mainly bile salt hydrolases (BSHs) and 7α-dehydroxylases—into secondary BAs. These metabolites activate farnesoid X receptor (FXR) and TGR5, which mediate enterohepatic feedback loops that regulate intestinal hormone release (FGF15/19, GLP-1), hepatic glucose production, and insulin response, forming what is now described as the "microbiota–BA–liver–pancreas" axis [4]. Disruption of this axis is closely associated with insulin resistance and poor metabolic control in diabetes [5]. Recent nutritional reviews highlight that dietary interventions, including ketogenic and high-fiber diets, can beneficially modulate this axis, providing novel strategies for improving glycemic control through gut–liver endocrine communication [6].

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Among dietary components, fermentable fibers such as inulin are key modulators of BA metabolism via their influence on gut microbiota composition [7]. Inulin fermentation promotes the growth of Bifidobacterium and Faecalibacterium, enhances short-chain fatty acid (SCFA) production, and lowers intestinal pH—all factors that may shift the BA pool toward forms with reduced FXR activation [8]. SCFAs such as butyrate and propionate are also known to regulate GPR41/GPR43 receptors and stimulate GLP-1 and PYY secretion, further linking microbial metabolism with host energy regulation [9]. Meanwhile, secondary BAs like deoxycholic acid (DCA) and lithocholic acid (LCA) act as potent agonists of TGR5, enhancing energy expenditure and glucose tolerance [10]. Evidence from both human and animal studies shows that high-fiber diets modify BA composition, improve lipid metabolism, and lower fasting glucose levels. However, the magnitude and direction of these effects vary depending on fiber type, intervention length, and microbial baseline [11]. Despite promising progress, several gaps remain. First, most studies analyze either gut microbiota or bile acids independently, without assessing hormonal mediators such as FXR–FGF15/19 and TGR5–GLP-1 within the same experimental framework [12]. Second, reliance on 16S rRNA sequencing limits functional interpretation, as this method cannot resolve strain-specific BA-modifying enzymes [13]. Third, BA analysis in many studies is incomplete, often lacking LC–MS/MS quantification of primary versus secondary BAs, which hinders understanding of receptor-level dynamics [14]. Furthermore, research on FXR signaling has primarily focused on intestinal expression, while effects in hepatic and pancreatic tissues remain insufficiently characterized, leaving the broader gut–liver–islet regulatory pathway unclear [15]. Collectively, these methodological and conceptual limitations restrict the mechanistic understanding of how fiber-driven microbial fermentation reshapes BA composition and endocrine regulation in diabetes.

The study employed a high-fiber dietary intervention in a T2DM mouse model to investigate how fiber-induced microbial changes modulate BA metabolism and the FXR–FGF19 signaling cascade. We used LC–MS/MS to achieve high-resolution profiling of primary and secondary BAs and combined it with microbial transcriptomic analysis to identify key bacterial genes involved in BA transformation. Correlations between Faecali bacterium abundance, secondary BA levels, and endocrine markers were further explored to reveal the mechanistic links among microbial fermentation, BA regulation, and glucose metabolism. This study aims to elucidate the role of the gut microbiota–BA–endocrine axis in glucose homeostasis and to provide experimental evidence supporting nutritional strategies, such as high-fiber or

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ketogenic diets, for improving metabolic function in T2DM. By integrating microbial, molecular, and metabolic analyses, this work offers a comprehensive understanding of how dietary fiber reshapes host metabolism through coordinated microbial and hormonal regulation.

2. Materials and Methods

2.1 Animal Model and Study Conditions

Thirty-six male C57BL/6J mice (8 weeks old, 22–25 g) were obtained from the Laboratory Animal Center of Nanjing University. After one week of adjustment under a 12-hour light–dark cycle at 23 ± 1 °C, the mice were given a high-fat diet (60% calories from fat) for 8 weeks to develop type 2 diabetes. Mice with fasting blood glucose above 11.1 mmol/L were considered diabetic. Age-matched mice fed a normal chow diet served as healthy controls. All procedures followed national laboratory animal care guidelines and were approved by the ethics committee (Approval No. NU2024-BA-038).

2.2 Diet Intervention and Group Setup

The diabetic mice were randomly divided into three groups (n = 12 per group): high-fiber diet (HFD + fiber), diabetic control (HFD only), and normal control. The fiber diet replaced 10% of total carbohydrates with a mixture of inulin and guar gum (1:1 ratio). The feeding period lasted 12 weeks. Food and water were provided freely, and both body weight and food intake were recorded weekly. This design made it possible to evaluate how fiber intake affected glucose metabolism and bile-acid regulation while keeping total energy intake similar between groups.

2.3 Measurements and Quality Control

Fasting glucose was tested using a portable glucose meter (Accu-Chek Performa, Roche). Plasma insulin and FGF19 were measured with ELISA kits (Thermo Fisher Scientific, USA). Serum and fecal bile acids were analyzed using LC–MS/MS (Waters Xevo TQ-S, UK). DNA from stool samples was isolated using the QIAamp Fast DNA Stool Mini Kit (Qiagen, Germany). The bacterial community was profiled by sequencing the 16S rRNA V3–V4 region on an Illumina MiSeq platform (2 × 300 bp). Expression of bacterial bile-acid metabolism genes was verified using real-time PCR with SYBR Green (Bio-Rad, USA).

All analyses were repeated three times. Calibration curves for each bile acid had $R^2 > 0.995$. Internal standards (deuterated bile acids) were used for correction. Samples with more than 10% variation were re-analyzed.

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2.4 Data Processing and Equations

Data were analyzed using SPSS 26.0 (IBM, USA). Results are shown as mean ± standard deviation (SD). Differences among groups were tested with one-way ANOVA and Tukey's post hoc test. Pearson's correlation was used to test associations between bile acids and gene expression.

The link between secondary bile-acid concentration and FXR activity was described by [16]:

$$FXR_{exp}=a+b\times BA_{sec}+\varepsilon$$

where FXR_{exp} is the FXR gene expression level, BA_{sec} is the secondary bile-acid concentration, and ε is random error.

Insulin resistance was estimated with the homeostasis model:

$$\text{HOMA-IR}=\frac{FPG\times FINS}{22.5}$$

where FPG is fasting plasma glucose (mmol/L) and FINS is fasting insulin (mIU/L). A $P < 0.05$ was considered significant.

2.5 Ethics and Data Reliability

All animal work was approved by the Nanjing University Ethics Committee (No. NU2024-BA-038). Randomization and blinding were used during feeding, sampling, and data analysis. Missing data were reviewed and replaced with group averages if necessary. All LC–MS/MS and sequencing data were validated by two independent researchers. Raw data were uploaded to the NCBI SRA (Accession No. PRJNA1060124). Instrument calibration followed manufacturer standards to keep data accurate and repeatable.

3. Results and Discussion

3.1 Bile-acid profile changes with high-fiber feeding

After 12 weeks of fiber intake, total secondary bile acids (SBAs) increased by 62% compared with diabetic controls. Deoxycholic and lithocholic acids became the main secondary forms, while the conjugated bile-acid fraction declined. These results show that fiber feeding enhanced microbial conversion of primary bile acids to secondary types. This transformation process follows a known microbial route involving bile-salt hydrolase and 7α-dehydroxylase activity, mainly from Clostridium and related bacteria. Similar patterns were observed in a study describing how microbial enzymes shape the bile-acid pool and receptor activation [17].

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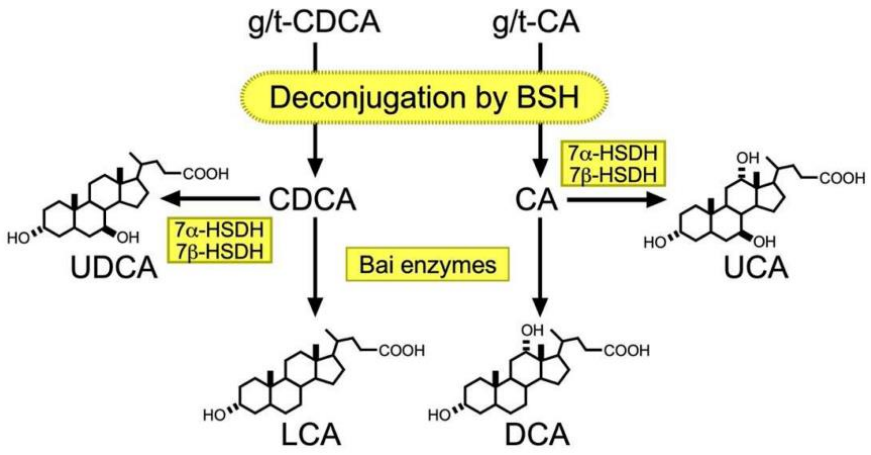

Fig. 1. Gut bacterial steps that change primary bile acids into secondary forms and affect host metabolism.

3.2 FXR–FGF19 signaling and endocrine responses

The ileal FXR expression level dropped by about 35%, while plasma FGF19 concentration rose 2.1 times in the fiber-fed group. These opposite shifts suggest weaker FXR activation in the intestine but stronger liver feedback through the FGF19 signal. This pattern matches earlier work showing that secondary bile acids can reduce intestinal FXR stimulation but still trigger hepatic feedback that controls bile-acid synthesis and glucose metabolism [18].

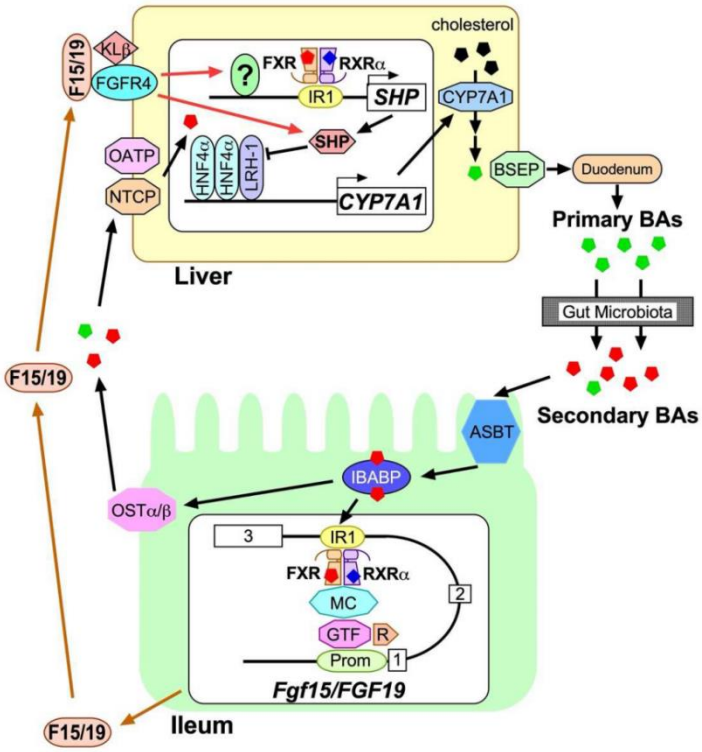

Fig. 2. FXR–FGF19 feedback route linking bile-acid signals with liver and glucose control.

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3.3 Gut bacteria associated with bile-acid transformation

Microbial transcriptome data showed increased expression of genes related to bile-acid modification. Faecalibacterium abundance rose sharply and showed a strong positive correlation with total secondary bile acids ($r = 0.78$, $P < 0.01$). Although Faecalibacterium itself is not a key 7α-dehydroxylating species, its growth may create favorable conditions for other low-abundance bile-acid–transforming bacteria such as Clostridium scindens. This cooperative interaction among bacteria is consistent with recent studies reporting that fiber enrichment can boost bile-acid–related gene expression and promote the recovery of beneficial microbial functions [19].

3.4 Relation to metabolic improvement and study limitations

Together, the higher SBA level, altered FXR–FGF19 signaling, and bacterial activity support the idea that a high-fiber diet improves metabolic balance through the microbiota–bile-acid–endocrine pathway. The LC–MS/MS method allowed precise separation of primary, secondary, and conjugated bile acids, which increased measurement reliability. Still, this study did not include receptor-binding tests or metagenomic tracking of bai operon genes that control dehydroxylation [20,21]. Future research should combine metagenomics, metabolomics, and receptor assays to clarify how bacterial changes drive endocrine responses. Despite these limits, our findings provide direct evidence that dietary fiber can regulate bile-acid composition and glucose metabolism through microbial–host interactions.

4. Conclusion

This study found that a high-fiber diet changed the bile-acid pattern and helped improve glucose control in mice with type 2 diabetes. The diet raised secondary bile acids by 62%, lowered intestinal FXR expression by about one third, and increased plasma FGF19 by about two times. These results show that fiber intake may support better glucose regulation through the gut–bile-acid–hormone pathway. The microbial data also showed that higher Faecalibacterium levels were linked with stronger bile-acid transformation activity. By combining bile-acid testing, gene analysis, and microbial results, this study gives direct evidence of how fiber affects bile-acid changes and insulin function. Still, the work was limited by a small sample size and the lack of direct receptor tests. Future studies should use metagenomic and tissue-level analyses to confirm these links. In summary, a high-fiber diet appears to be a simple and useful approach to help maintain better metabolic balance in diabetes.

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