Effects of *Lactobacillus acidophilus* on Hepatic and Microbial Dysregulation in MASLD and Diabetes

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Aim

Metabolic dysfunction-associated steatotic liver disease (MASLD) and type 2 diabetes (T2D) are closely linked to gut-liver axis dysfunction, yet the mechanistic contribution of gut microbiota remains incompletely defined. We investigated whether *Lactobacillus acidophilus* alleviates hepatic and metabolic abnormalities through modulation of gut microbiota and downstream metabolic pathways.

Methods

Human stool samples were collected from healthy controls (HC, n=131), healthy controls with diabetes (HC+DM, n=91), atients with metabolic dysfunction-associated steatohepatitis (MASH, n=133), and patients with MASH and diabetes (MASH+DM, n=51), and microbial composition was analyzed by 16S rRNA profiling. *L. acidophilus*, identified from the human cohort analysis, was further evaluated in Western diet (WD)-fed mice and ob/ob diabetic mice. Mice received oral gavage of *L. acidophilus* (1×10^9 CFU, twice weekly), with metformin as a positive control. Hepatic histology, serum biochemical parameters, oral glucose tolerance test, qPCR, and microbiome profiling were performed.

Conclusion

L. acidophilus improved hepatic steatosis, lipid dysregulation, and glucose intolerance across MASLD and T2D models, supporting its potential as a microbiome-based therapeutic candidate through gut microbiota modulation and AMPK-associated metabolic regulation.

Result

In the human cohort, dysbiosis worsened with disease severity, and *Lactobacillus* abundance decreased from HC to MASH. Notably, among *Lactobacillus* species examined, *L. acidophilus* uniquely exhibited an early and significant decrease in HC+DM compared with HC (P<0.01). In WD-fed mice, *L. acidophilus* reduced hepatic steatosis and inflammatory injury (NAS: NCD, 0; WD, 7.1; La, 5.2) and significantly lowered hepatic cholesterol levels (p = 0.0486). *L. acidophilus* restored intestinal barrier markers, reduced hepatic inflammation, and regulated lipid metabolism, accompanied by partial recovery of WD-induced dysbiosis. In ob/ob diabetic mice, *L. acidophilus* improved glucose homeostasis (OGTT AUC: Con, 45733; La, 36888; Met, 36510). *L. acidophilus* also enhanced hepatic AMPK activation, consistent with reduced lipogenesis and gluconeogenesis.

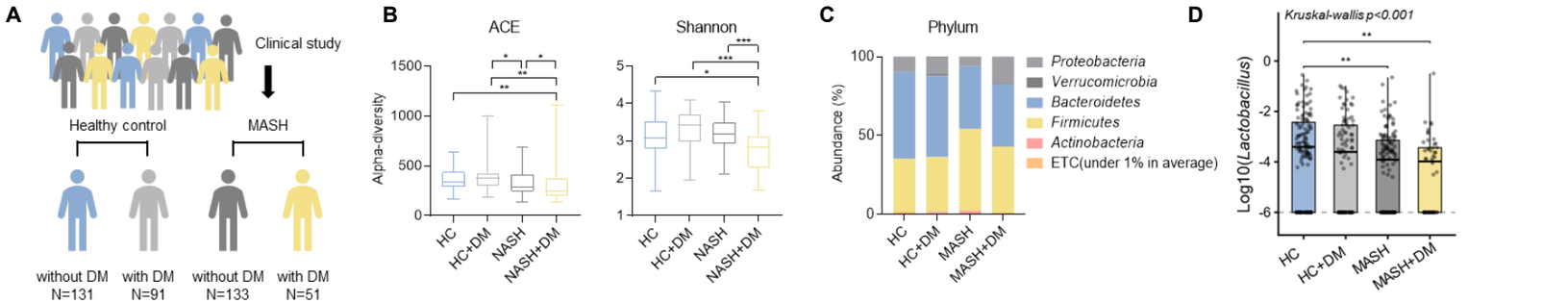

Figure 1. Human cohort gut microbiome profiling according to liver disease and diabetes status. (A) Schematic of the clinical study design. (B) The relative abundance of alpha diversity including the ACE index and Shannon. (C) Phylum-level community composition shown as relative abundance. (F) Genus-level *Lactobacillus* relative abundance in the study cohort (n=406).

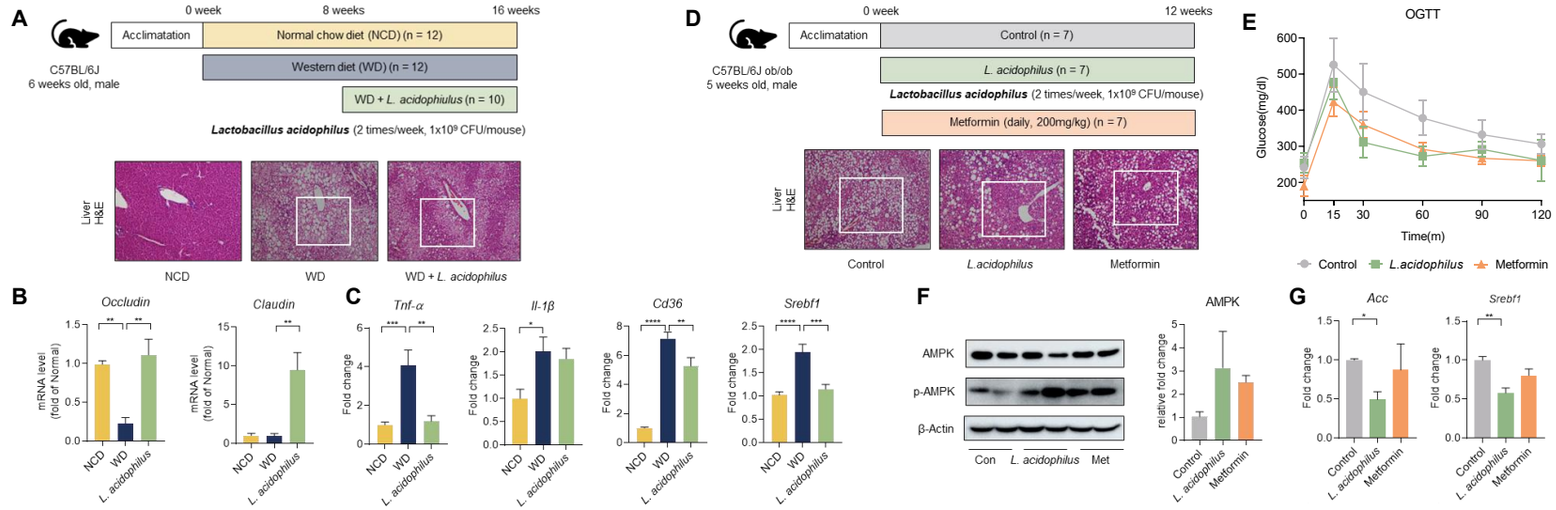

Figure 2. Effects of *L. acidophilus* in WD-fed and ob/ob mouse models.(A) Schematic of the clinical study design. (A) Experimental scheme and liver histology in WD-fed mice.(B) Hepatic tight-junction gene expression. (C) Hepatic inflammatory and lipid metabolism–related gene expression. (D) Experimental scheme and liver histology in ob/ob mice. (E) OGTT. (F) Western blot analysis of AMPK phosphorylation. (G) Hepatic metabolic gene expression. Data are presented as mean ± SEM. *P < 0.05, **P < 0.01.