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Differential Effects of Milk, Yogurt, and Cheese on Insulin Sensitivity, Hepatic Function, and Gut Microbiota in Diet-Induced Obese Mice

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The prevalence of obesity and associated metabolic disorders, such as insulin resistance (IR) and fatty liver disease (steatosis), is often linked to a high-fat Western diet. Recent meta-analyses indicate that dairy consumption may mitigate these effects, particularly favoring low-fat dairy products. However, the underlying molecular mechanisms remain elusive. Dairy products vary in nutrient composition (calcium, fat) and structure, impacting digestion and nutrient absorption. Fermentation processes in cheese and yogurt introduce bacterial cultures with potentially positive metabolic effects. This study investigates the distinct effects of different dairy subgroups on insulin sensitivity, liver function, and gut microbiota in diet-induced obese mice, exploring potential mechanisms for mitigating Western diet-induced metabolic dysfunction.

C57BL/6 mice (n = 16/group) were fed a high-fat diet (HFD, 45% fat) mimicking a Western diet rich in saturated fatty acids (SFA), or HFD supplemented with: fat-free milk (MILK), fat-free yogurt (YOG), or reduced-fat cheese (CHE, 19% fat) for 8 weeks. These supplements were administered daily at 10% of total caloric intake, reflecting typical U.S. dietary patterns. We assessed insulin resistance using the insulin tolerance test (ITT) and the homeostasis model assessment (HOMAIR). Weekly monitoring of food and water intake and body weight was conducted. After euthanasia, liver tissue was collected for Western blot analysis of key proteins in insulin signalling, gluconeogenesis, lipogenesis, lipid oxidation, uptake, and release pathways. Comprehensive lipidomics profiling of the liver and serum was performed using LC-MS, and fecal samples were analyzed for microbial diversity via 16S rRNA sequencing. Statistical analyses included QIIME2DEseq2, MetaboAnalyst 5.0, and MicrobiomeAnalyst. One-way and two-way ANOVA with Tukey's post-hoc test were performed.

The MILK and YOG interventions significantly reduced body weight, fat mass, and epididymal fat pad weight ($p < 0.05$) compared to HFD alone. Enhancements in glucose clearance and insulin sensitivity were notable in the MILK and YOG groups, with associated upregulations in glycogen synthase (GS), phosphoenolpyruvate carboxykinase (PEPCK), and protein kinase B (AKT) signaling. Regarding hepatic steatosis, MILK and YOG increased protein levels involved in fatty acid oxidation (ACSL, CPT1) and lowered PPARγ, suggesting reduced fat storage. Additionally, higher AMPK, PPARα, ATGL, and HSL protein abundances supported enhanced fatty acid breakdown. Gut microbiota analyses revealed a higher bacterial species richness in the MILK and YOG groups, with distinct fecal microbiota compositions across all dairy interventions. Lipidomics identified unique and shared metabolic markers among the groups, implicating glycerolipid, glycerophospholipid, sphingomyelin metabolism, and inflammatory pathways.

This study demonstrates that different dairy products uniquely modulate metabolic health markers in diet-induced obese mice. Milk and yogurt particularly promote improved insulin sensitivity and hepatic functions, potentially mediated through alterations in metabolic pathways and gut microbiota composition.

References

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