Fasting-mimicking diet offers new ways for crohn's diseases management

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The management of Crohn's disease (CD) has long hinged on immunosuppressive therapies—an approach that often poses a delicate risk–benefit dilemma, especially for patients with milder forms of the disease. Now, a randomized controlled trial[1] by Kulkarni et al., published in Nature Medicine, offers a compelling alternative in which a periodic fasting-mimicking diet (FMD) can effectively induce clinical remission and reduce intestinal inflammation in individuals with mild-to-moderate CD. The open-label trial randomized 97 adults with mild-to-moderate CD (CDAI 151–450)in a 2:1 ratio to three monthly cycles of a five-day FMD or to the continued baseline diet. At week 12, 69.2% of FMD participants achieved clinical response (CDAI decrease ≥ 70 or ≤ 150) versus 43.8% of control group(P=0.03)，and the clinical remission (CDAI ≤ 150) was attained by 64.6% versus 37.5% (P = 0.02).

Table 1. Comparison of dietary interventions for mild-to-moderate crohn's disease.

Feature	FMD (Kulkarni et al.)	CDED-AD (Yanai et al.)	IBDMED (Abreu et al.)	"Tasty & Healthy" (Aharoni-Frutkoff et al.)
Intervention structure	Intermittent (5 days/month)	Continuous	Continuous	Continuous
Duration	3 months (3 cycles)	24 weeks	Under investigation	8 weeks
Dietary composition	Plant-based, low calorie, high unsaturated fat	Exclusion of animal fat, emulsifiers, processed foods	High olive oil, fatty fish, fiber, plant foods	Unprocessed whole foods, avoidance of ultra-processed products
Mechanistic rationale	Fasting physiology, metabolic reprogramming, periodic gut rest	Elimination of pro-inflammatory dietary components	Anti-inflammatory dietary pattern, microbiome modulation	Whole food-based anti-inflammatory effects
Clinical remission rate (ITT)	64.6% (week 12, CDAI≤ 150)	35% (week 24, endoscopic remission)	Under investigation	56% (week 8, symptomatic remission)
Fecal calprotectin reduction	22.0% mean reduction	Not reported	Not reported	Not reported
Adherence rate	76.9% (completed all cycles)	72% (completed per protocol at week 6)	Under investigation	88% (tolerated intervention)
Key strength	Intermittent structure, high adherence, mechanistic biomarker data	Evidence for sustained remission	Broadly acceptable dietary pattern	High palatability, rapid response
Key limitation	Requires commercial meal kits, limited long-term data	Complex elimination rules, requires dietitian support	Longer-term outcomes pending	Limited mechanistic data

Table 1. Comparison of Dietary Interventions for Mild-to-Moderate Crohn's Disease. Data are derived from the respective trials as published. ITT, intention-to-treat. Clinical remission definitions vary: FMD (CDAI ≤ 150), CDED-AD (endoscopic remission), "Tasty & Healthy" (symptomatic remission). Adherence definitions: FMD (completed all three cycles), CDED-AD (per-protocol at week 6), "Tasty & Healthy" (study completion). Fecal calprotectin reduction was reported only in the FMD trial. Under investigation indicates outcomes not yet reported.

Fecal calprotectin decreased by a mean of 22.0% in the FMD arm while rising 8.0% in the controls (P = 0.03), and 37.0% of FMD participants achieved ≥ 50% reduction in fecal calprotectin versus 6.3% of controls (P = 0.01). Subgroup analyses revealed greater efficacy in patients with colonic (82.4% response) and ileocolonic (71.4%) disease, but not in those with isolated ileal involvement (55.5% vs60.0%; P = 0.99). Adherence was high (76.9% completed all cycles), with no serious adverse events occurred in the FMD group; fatigue (52.3%) and headache (50.8%) were common but mild.

The FMD evaluated by Kulkarni et al. comprises a commercially available, plant-based, calorie-restricted regimen consumed over five consecutive days each month. On Day 1, participants were provided approximately 1,090 kcal, consisting of 10% protein, 56% fat, and 34% carbohydrates; On Days 2 through 5 offered approximately 725 kcal daily, with a macronutrient composition of 9% protein, 44% fat, and 47% carbohydrates. The diet includes a variety of meals such as soups, nutrition bars, snacks, and other dietary supplements, all designed to simulate the effects of fasting while ensuring adequate micronutrient intake. A critical and unresolved question pertains to whether the benefits of the FMD are attributable solely to caloric restriction or whether the specific composition of the diet—particularly its high levels of unsaturated fats and prebiotic oligofructose—contributes independently to these effects. Preclinical studies indicated that these components may promote beneficial gut microbiota and mitigate inflammation， however, empirical data from human studies remain scarce. Future factorial trials that compare the FMD to isocaloric control diets with equivalent macronutrient profiles could elucidate these underlying mechanisms.

FMD joins a growing list of dietary strategies for CD, yet its intermittent structure distinguishes it from continuous approaches (Table 1). The Crohn's disease exclusion diet for adults (CDED-AD)[2] requires sustained elimination of specific food components and achieved 35% endoscopic remission at week 24. The Mediterranean diet (IBDMED)[3] emphasizes inclusion of anti-inflammatory foods but awaits long-term outcome data. The whole-food "Tasty & Healthy" diet[4] reported 56% symptomatic remission at 8 weeks in a

single-arm study. FMD's key advantage lies in its periodic nature: only five days per month of structured meal provision, after which patients can resume their usual diet. This design addresses the major translational barrier of long-term sustainability, as reflected in the 76.9% adherence rate. However, the open-label design and subjective CDAI endpoint warrant cautious interpretation; placebo effects may be substantial, particularly in mild disease.

FMD likely exerts its therapeutic effects through four interconnected pathways. Metabolic and lipid mediator reprogramming is central: caloric restriction elevates β-hydroxybutyrate, which inhibits the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome. Untargeted metabolomics in the trial revealed coordinated downregulation of pro-inflammatory arachidonic acid-derived leukotrienes, including leukotriene B_4 (LTB_4) and leukotriene E_4 (LTE_4), as well as oxidized linoleic acid metabolites—hydroxyoctadecadienoic acids (HODEs) and trihydroxyoctadecenoic acids (TriHOMEs)—alongside upregulation of anti-inflammatory lipoxins, specifically 15-oxo-lipoxin A_4/B_4 (15-oxo-LXA_4/LXB_4). Immune-effector transcript suppression was evident in peripheral blood mononuclear cells (PBMCs), with reduced expression of NLRP3, interleukin-1β (IL-1β), interleukin-18 (IL-18), tumor necrosis factor (TNF), and the chemokines C-C motif chemokine ligand 20 (CCL20) and C-X-C motif chemokine ligand 10 (CXCL10), thereby attenuating inflammatory cell recruitment. Gut microbiota remodeling—supported by preclinical data—involves prebiotic components promoting outgrowth of beneficial taxa like Lactobacillusaceae, which regulate T-cell activity.[5] Finally, epithelial barrier enhancement occurs through fasting-induced autophagy, post-refeeding intestinal stem cell activation, and reduced luminal antigenic drive during fasting periods, collectively facilitating mucosal healing.

The trial's subgroup findings suggest FMD is most effective in colonic and inflammatory (non-stricturing) phenotypes, while isolated ileal disease derived minimal benefit. Ideal candidates may include patients with mild-to-moderate colonic CD who prefer non-pharmacologic options or are ineligible for immunosuppressive therapy. Contraindications include undernutrition, pregnancy, nut allergies, diabetes treated with hypoglycemic agents, severe cardiovascular disease, and short bowel syndrome. Safety in elderly patients and those with severe disease remains unstudied. Although FMD was well tolerated, the five-day caloric restriction may cause transient fatigue and headache. Therefore, monitoring for weight loss and medication interactions is prudent.

The open-label design is the most important limitation, as CDAI includes subjective components susceptible to bias. The modest sample size (n=97) and short follow-up (three months) preclude conclusions about durability. Notably, clinical response was lost after a three-month washout, indicating that therapeutic benefits may attenuate following FMD discontinuation and that sustained remission likely requires periodic re-intervention. However, the optimal frequency and duration of such maintenance cycles remain undefined—a critical knowledge gap requiring prospective investigation. The predominantly white cohort limits generalizability, and endoscopic data were insufficient for quantitative analysis. Future research must prioritize multicenter, double-blind trials with sham dietary controls and blinded endpoint assessment. Long-term studies are needed to define optimal maintenance regimens (e.g., monthly versus quarterly cycles) and assess safety beyond three months. Comparative effectiveness trials against established dietary and pharmacologic interventions will clarify FMD's therapeutic position. Mechanistic studies incorporating mucosal immunophenotyping and microbiome profiling could identify response predictors. Exploring FMD alongside biologic agents (like anti-TNF and anti-integrin) may uncover synergistic effects that reduce drug needs or improve remission rates. Tailored nutrition strategies based on disease location, microbial composition, or metabolic profiles could also enhance results.

Kulkarni and colleagues provide compelling initial evidence that FMD can induce clinical and biochemical remission in mild-to-moderate CD, with a favorable safety profile and high adherence. The integrated mechanisms of metabolic reprogramming, immune modulation, microbiota remodeling, and epithelial repair provide a plausible biological basis. However, these findings are from a single open-label trial and are hypothesis-generating. If validated in rigorous future studies, including those identifying optimal maintenance strategies, FMD could become a crucial non-pharmacologic tool for CD management. For now, cautious optimism and further research are necessary.

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DECLARATION OF INTERESTS

The authors declare no competing interests.