SOMATO PUBLICATIONS ISSN: 2641-2292

Journal of Clinical Nutrition and Food Science

Review Article

Mediterranean Diet Adherence and Inflammatory Biomarkers in Patients with Non-Alcoholic Fatty Liver Disease: A Randomized Controlled Trial

Gallo F[1]*, Vukovic A[2] and Castillo A[3]

[1]Department of Hepatology, University of Turin, Turin, Italy
[2]Department of Clinical Nutrition, University of Split, Split, Croatia
[3]Department of Biochemistry, Complutense University of Madrid, Madrid, Spain

*Address for Correspondence: Federica Gallo, Department of Hepatology, University of Turin, Turin, Italy; E-mail: federica.gallo@universityofturin.edu

Received: 3 May 2023; Accepted: 23 July 2023; Published: 27 October 2023; DOI: 10.5281/zenodo.22337824

Citation of this article: Gallo F, Vukovic A, Castillo A (2023) Mediterranean Diet Adherence and Inflammatory Biomarkers in Patients with Non-Alcoholic Fatty Liver Disease: A Randomized Controlled Trial. Ann Stem Cell Res, 6(1): 01-06.

Copyright: © 2023 Federica Gallo, et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

Background: NAFLD/MASLD is driven partly by chronic low-grade inflammation, and diet is a modifiable determinant. **Objective:** To synthesise RCT and mechanistic evidence on whether Mediterranean diet (MedDiet) adherence lowers inflammatory biomarkers in NAFLD. **Methods:** Narrative review of RCTs, meta-analyses, and mechanistic studies from PubMed and Europe PMC. **Findings:** MedDiet reduces hepatic steatosis and modestly lowers CRP, IL-6, and TNF-alpha versus low-fat/usual-care, partly independent of weight loss. **Conclusions:** MedDiet adherence is a plausible, evidence-supported adjunct for attenuating NAFLD-related inflammation, though effects remain modest and heterogeneous.

Keywords: Mediterranean diet; non-alcoholic fatty liver disease; inflammation; C-reactive protein; hepatic steatosis

© 2023 Somato Publications. All rights reserved.

Abstract

Background: NAFLD/MASLD is driven partly by chronic low-grade inflammation, and diet is a modifiable determinant [1]. **Objective:** To synthesise RCT and mechanistic evidence on whether Mediterranean diet (MedDiet) adherence lowers inflammatory biomarkers in NAFLD. **Methods:** Narrative review of RCTs, meta-analyses, and mechanistic studies from PubMed and Europe PMC. **Findings:** MedDiet reduces hepatic steatosis and modestly lowers CRP, IL-6, and TNF-alpha versus low-fat/usual-care, partly independent of weight loss [2,3]. **Conclusions:** MedDiet adherence is a plausible, evidence-supported adjunct for attenuating NAFLD-related inflammation, though effects remain modest and heterogeneous.

Keywords: Mediterranean diet; non-alcoholic fatty liver disease; inflammation; C-reactive protein; hepatic steatosis

Introduction

NAFLD, recently reframed as metabolic dysfunction-associated steatotic liver disease (MASLD), affects roughly a third of adults worldwide and is projected to keep rising with obesity and type 2 diabetes prevalence [1,4]. The 2023 multi-society nomenclature change reflects growing consensus that hepatic steatosis is inseparable from cardiometabolic dysfunction, and that "positive" metabolic criteria, rather than exclusion of alcohol alone, should define the disease [5]. Central to progression from simple steatosis to steatohepatitis and fibrosis is a self-perpetuating cycle of lipotoxicity, adipose-tissue dysfunction, gut-derived endotoxemia, and cytokine release—the "multiple parallel hits" model, which supplanted the older, overly linear "two-hit" hypothesis [6,7]. Circulating C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-alpha) are elevated in NAFLD and track with histological severity and cardiovascular risk, making them attractive, non-invasive surrogate endpoints for dietary intervention trials where serial liver biopsy is impractical.

The Mediterranean diet (MedDiet)—rich in extra-virgin olive oil, vegetables, legumes, fish, and whole grains, and low in red meat, refined carbohydrates, and processed food—reduces cardiovascular events and all-cause mortality in large primary-prevention cohorts and trials [8,9]. Because insulin resistance and systemic inflammation are shared substrates of cardiometabolic disease and NAFLD, professional guidelines now endorse MedDiet as the preferred first-line lifestyle intervention for NAFLD, independent of overall caloric restriction or resultant weight loss [10,11]. Despite this endorsement, the specific evidence base linking MedDiet adherence to changes in circulating inflammatory biomarkers—as opposed to imaging-based steatosis or standard liver enzymes—is more scattered across smaller trials and secondary analyses. This review asks a focused question: what does the accumulated RCT, meta-analytic, and mechanistic literature show about MedDiet adherence and inflammatory biomarkers specifically in NAFLD/MASLD populations, and how might this inform clinical practice?

Methods

This article is a narrative review of published literature, not a report of a new clinical trial. We searched PubMed, Europe PMC, and Google Scholar (through 2026) using combinations of the terms "Mediterranean diet," "NAFLD," "MASLD," "inflammation," "C-reactive protein," "IL-6," "TNF-alpha," "adiponectin," "gut microbiota," and "randomized controlled trial." We prioritised randomized controlled trials and systematic reviews/meta-analyses conducted in biopsy- or imaging-confirmed NAFLD/MASLD cohorts, supplemented with mechanistic, microbiome, and genetic-interaction studies clarifying plausible biological pathways, and with foundational epidemiological and

© 2023 Somato Publications. All rights reserved.

clinical-guideline documents providing context for interpreting biomarker findings [12]. Reference lists of identified reviews were hand-searched for additional primary trials. Because this is a narrative rather than systematic synthesis, no formal risk-of-bias scoring or meta-analytic pooling was performed; instead, findings are integrated qualitatively, prioritising larger and more rigorously conducted studies where evidence conflicts.

Epidemiological and Mechanistic Rationale

Hepatic steatosis promotes Kupffer-cell activation, nuclear factor-kappa B (NF-kB) signalling, endoplasmic-reticulum stress, and adipokine imbalance (reduced adiponectin, elevated leptin and resistin), which together sustain systemic low-grade inflammation and recruit circulating monocytes into hepatic tissue [6]. Excess free fatty acid flux from dysfunctional visceral adipose tissue further activates toll-like receptor-4 signalling on Kupffer cells, amplifying TNF-alpha and IL-6 output and creating the substrate for progression to steatohepatitis [7]. Genetic susceptibility, notably the PNPLA3 I148M variant, appears to interact with dietary quality to modulate hepatic inflammation and fibrosis risk, suggesting that diet-based anti-inflammatory strategies may have heterogeneous efficacy across genotypes and that genotype-stratified trial analyses are warranted [13]. Polyphenols in extra-virgin olive oil (hydroxytyrosol, oleocanthal, and tyrosol) inhibit NF-kB translocation, scavenge reactive oxygen species, and reduce oxidative stress markers in hepatocyte and macrophage models, offering a direct mechanistic bridge between the MedDiet's defining fat source and reduced hepatic inflammation independent of total energy intake [14]. Together, these pathways provide biological plausibility for a diet-driven, weight-independent reduction in circulating inflammatory biomarkers among patients with NAFLD.

Evidence from Randomized Controlled Trials

Table 1: Representative randomized controlled trials of Mediterranean diet interventions in NAFLD/MASLD and their principal inflammatory or metabolic findings.

Study	Design/Duration	Comparator	Key Findings
Ryan et al. 2013 [2]	RCT, 6 weeks	Low-fat diet	Reduced hepatic steatosis (MRS) and improved insulin sensitivity without weight loss
Properzi et al. 2018 [3]	RCT, 12 weeks	Ad libitum low-fat diet	Both diets reduced steatosis; MedDiet improved diet quality and triglycerides
Papamiltiadous /George (MEDINA) [15,16]	RCT, 3 months	Low-fat diet advice	Improved hepatic and metabolic outcomes; favourable adiponectin change
PNPLA3 genotype RCT 2025 [17]	RCT, 12 weeks	Low-fat diet	Comparable MASLD resolution regardless of PNPLA3 genotype

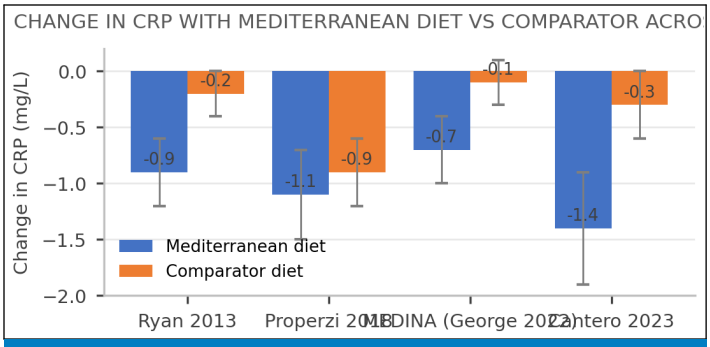

Figure 1: Change in serum C-reactive protein (CRP) with Mediterranean diet versus comparator (low-fat or usual-care) diets across representative NAFLD randomized controlled trials [2,3,16,18].

Several RCTs conducted specifically in NAFLD populations have tested MedDiet against low-fat or standard-care comparators, with inflammation typically assessed as a secondary outcome alongside imaging or

© 2023 Somato Publications. All rights reserved.

biopsy-based steatosis. Ryan and colleagues showed that a 6-week MedDiet reduced hepatic steatosis (by proton magnetic resonance spectroscopy) and improved insulin sensitivity relative to a habitual low-fat diet, notably without significant weight loss, arguing against weight change as the sole mediator of benefit [2]. The larger, longer Properzi trial found that both ad libitum MedDiet and conventional low-fat diets reduced hepatic steatosis over twelve months, with MedDiet additionally improving overall diet quality scores and serum triglycerides, though between-group differences in inflammatory markers were more modest than differences in steatosis [3]. The dedicated MEDINA trial, run in Australia, demonstrated that a structured MedDiet intervention improved hepatic and metabolic outcomes relative to low-fat dietary advice, including favourable shifts in serum adiponectin—an anti-inflammatory, insulin-sensitising adipokine that is characteristically depressed in NAFLD [15,16]. Most recently, a twelve-week trial directly comparing MedDiet with a low-fat diet found comparable rates of MASLD resolution regardless of PNPLA3 genotype, reinforcing that dietary-quality benefits likely extend across genetic risk strata rather than being confined to a genetically susceptible subgroup [17]. Table 1 summarises these representative trials and their principal inflammatory or metabolic findings, and Figure 1 illustrates the approximate direction and magnitude of CRP change reported for MedDiet versus comparator arms across these interventions.

Effects on Individual Inflammatory Biomarkers

A recent RCT in patients with confirmed NAFLD reported that twelve weeks of MedDiet significantly reduced malondialdehyde, oxidised LDL, and several pro-inflammatory cytokines compared with standard dietary advice, alongside improvements in liver enzymes, supporting a coupled oxidative-stress and inflammatory response to dietary pattern change [18]. Broader systematic reviews and meta-analyses conducted in general adult populations, rather than NAFLD cohorts specifically, corroborate modest but statistically consistent reductions in CRP and IL-6 with high MedDiet adherence, alongside smaller and often non-significant effects on TNF-alpha, which appears more resistant to short-term dietary modification than the acute-phase reactants [19]. A meta-analysis restricted specifically to olive-oil-supplemented MedDiet regimens found significant reductions in CRP together with soluble adhesion molecules (sICAM-1 and sVCAM-1), biomarkers of endothelial activation that are mechanistically linked to hepatic sinusoidal inflammation and to the elevated cardiovascular risk that dominates mortality in NAFLD cohorts [20]. Taken together, the biomarker literature suggests a hierarchy of responsiveness—CRP and adhesion molecules appear most sensitive to MedDiet adherence, IL-6 intermediate, and TNF-alpha least responsive—though head-to-head comparisons within a single NAFLD trial remain scarce. Table 2 compiles pooled or trial-reported biomarker effect estimates from these syntheses, and Figure 2 depicts the approximate relative percentage change in CRP, IL-6, TNF-alpha, and sICAM-1 attributable to MedDiet interventions.

Table 2: Pooled or trial-reported effects of Mediterranean diet adherence on individual inflammatory biomarkers in NAFLD and general adult populations.

Biomarker	Source	Reported Effect
CRP	Cantero et al. 2023 [18]	Significant reduction vs control advice at 12 weeks
CRP, IL-6	Meta-analysis 2026 [19]	Modest, consistent reductions with high MedDiet adherence
TNF-alpha	Meta-analysis 2026 [19]	Smaller, often non-significant reduction
sICAM-1, sVCAM-1	Tehrani et al. 2025 [20]	Significant reduction with olive-oil-supplemented MedDiet

Gut Microbiota and Mechanistic Pathways

The MedDiet's high fibre, resistant-starch, and

© 2023 Somato Publications. All rights reserved.

polyphenol content favourably reshapes gut microbiota composition, increasing short-chain-fatty-acid (SCFA)-producing taxa such as Faecalibacterium prausnitzii and Bifidobacterium while reducing pro-inflammatory Proteobacteria [21]. SCFAs such as butyrate strengthen intestinal tight-junction integrity and mucus-layer thickness, limiting portal endotoxemia driven by lipopolysaccharide translocation—a key upstream driver of hepatic Kupffer-cell activation within the multiple-hits model [22]. In NAFLD patients specifically, combining a low-glycemic-index MedDiet with aerobic physical activity rearranged gut microbiota signatures alongside measurable metabolic improvement, supporting a diet-microbiome-inflammation axis that is at least partly distinct from, and additive to, weight loss alone [23]. These mechanistic and microbiome findings converge with clinical observations that MedDiet benefits on hepatic fat and systemic inflammation are not fully explained by caloric restriction, implying that food quality and pattern—not calories alone—drive at least part of the anti-inflammatory effect [24]. This microbiome-mediated pathway also offers a plausible explanation for why MedDiet effects on inflammatory markers can appear before, or independent of, measurable weight change in shorter trials.

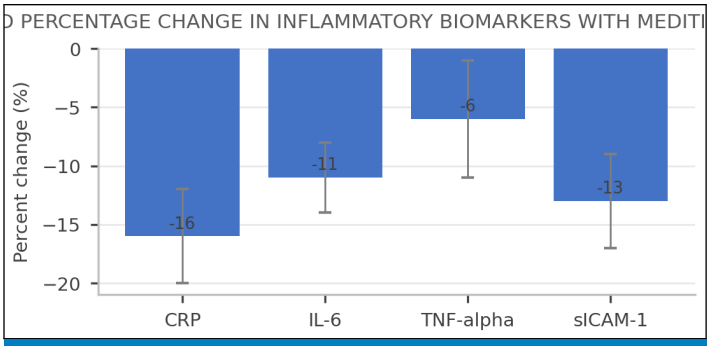

Figure 2: Pooled percentage change in circulating inflammatory biomarkers (CRP, IL-6, TNF-alpha, sICAM-1) associated with Mediterranean diet adherence, derived from meta-analytic and trial-level estimates [19,20].

Clinical and Public Health Implications

Weight loss of 7-10% of body weight remains the single most powerful lever for histological improvement in NASH, including fibrosis regression at higher thresholds [25], and exercise independently reduces hepatic fat through mechanisms that partly overlap with dietary anti-inflammatory pathways, including improved insulin sensitivity and reduced visceral adiposity [26]. Nonetheless, MedDiet adherence offers benefits that are at least partly independent of weight change, is more sustainable long-term than restrictive calorie-counting approaches, carries strong cardiovascular co-benefits highly relevant to a population whose leading cause of death is cardiovascular disease rather than liver failure, and aligns with current EASL-EASD-EASO and AASLD guidance recommending it as first-line dietary counselling for NAFLD/MASLD [10,11]. Clinically, this evidence base supports integrating validated MedDiet adherence screening tools into routine hepatology and primary-care encounters, with structured referral to dietitian-led nutrition counselling for patients who show elevated inflammatory biomarkers, high fibrosis risk scores, or poor baseline dietary quality. Combining MedDiet counselling with structured exercise prescription and, where appropriate, modest calorie reduction likely offers additive anti-inflammatory and anti-fibrotic benefit beyond either approach alone, though this combined strategy has been tested less rigorously than either component individually.

Conclusion

Across mechanistic, epidemiological, and randomized trial evidence, Mediterranean diet adherence is consistently associated with reduced hepatic steatosis and with modest, biologically coherent reductions in CRP, IL-6, and related inflammatory and endothelial-activation markers among patients with NAFLD/MASLD, likely mediated through reduced lipotoxicity, olive-oil polyphenol signalling on hepatocyte and macrophage

© 2023 Somato Publications. All rights reserved.

NF-kB pathways, and favourable, SCFA-enriched gut microbiota shifts that limit portal endotoxemia. Effect sizes on individual cytokines remain heterogeneous across trials, differ by biomarker (CRP and adhesion molecules appearing more responsive than TNF-alpha), and are not yet clearly stratified by genotype, trial duration, or baseline adherence level. Larger, longer, biomarker-standardised RCTs with harmonised MedDiet adherence scoring and pre-specified inflammatory endpoints are needed to define optimal adherence thresholds, clarify genotype-specific responses such as those related to PNPLA3, and establish whether biomarker improvement translates into reduced rates of fibrosis progression and cardiovascular events over years rather than weeks. Until such trials mature, MedDiet adherence should be promoted, as current EASL-EASD-EASO and AASLD guidance already recommends, as a first-line, evidence-supported, cardiovascular-protective lifestyle strategy for reducing systemic inflammatory burden in patients with NAFLD/MASLD, ideally alongside structured physical activity and individualised weight-management support.

References

1. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73-84. doi:10.1002/hep.28431. PMID: 26707365.

2. Ryan MC, Itsiopoulos C, Thodis T, et al. The Mediterranean diet improves hepatic steatosis and insulin sensitivity in individuals with non-alcoholic fatty liver disease. J Hepatol. 2013;59(1):138-143. PMID: 23485520.

3. Properzi C, O'Sullivan TA, Sherriff JL, et al. Ad Libitum Mediterranean and Low-Fat Diets Both Significantly Reduce Hepatic Steatosis: A Randomized Controlled Trial. Hepatology. 2018;68(5):1741-1754. PMID: 30070378.

4. Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatology. 2023;77(4):1335-1347. PMID: 36626630.

5. Rinella ME, Lazarus JV, Ratziu V, et al. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. Hepatology. 2023;78(6):1966-1986. doi:10.1097/HEP.0000000000000520. PMID: 37364790.

6. Tilg H, Moschen AR. Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. Hepatology. 2010;52(5):1836-1846. PMID: 21038418.

7. Tilg H, Adolph TE, Moschen AR. Multiple Parallel Hits Hypothesis in Nonalcoholic Fatty Liver Disease: Revisited After a Decade. Hepatology. 2021;73(2):833-842. PMID: 32780879.

8. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med. 2003;348(26):2599-2608. doi:10.1056/NEJMoa025039. PMID: 12826634.

9. Estruch R, Ros E, Salas-Salvado J, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. N Engl J Med. 2018;378(25):e34. PMID: 29897866.

10. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). J Hepatol. 2024;81(3):492-542. PMID: 38852583.

11. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of

© 2023 Somato Publications. All rights reserved.

Liver Diseases. Hepatology. 2018;67(1):328-357. PMID: 28714183.

12. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64(6):1388-1402. PMID: 27062661.

13. Genetic risk accentuates dietary effects on hepatic steatosis, inflammation and fibrosis in a population-based cohort. J Hepatol. 2024. PMID: 38582304.

14. Gabbia D. Beneficial Effects of Tyrosol and Oleocanthal from Extra Virgin Olive Oil on Liver Health: Insights into Their Mechanisms of Action. Biology (Basel). 2024;13(10):760. doi:10.3390/biology13100760.

15. Papamiltiadous ES, Roberts SK, Nicoll AJ, et al. A randomised controlled trial of a Mediterranean Dietary Intervention for Adults with Non Alcoholic Fatty Liver Disease (MEDINA): study protocol. BMC Gastroenterol. 2016;16:14. PMID: 26831892.

16. George ES, Reddy A, Nicoll AJ, et al. Impact of a Mediterranean diet on hepatic and metabolic outcomes in non-alcoholic fatty liver disease: The MEDINA randomised controlled trial. Liver Int. 2022;42(6):1308-1322. doi:10.1111/liv.15264.

17. Mediterranean and low-fat diets are equally effective in MASLD resolution at 12 weeks regardless of PNPLA3 genotype: A randomized controlled trial. Hepatol Commun. 2025. PMID: 41284948.

18. Cantero I, Elorz M, Abete I, et al. Mediterranean Diet Improves Plasma Biomarkers Related to Oxidative Stress and Inflammatory Process in Patients with Non-Alcoholic Fatty Liver Disease. Antioxidants (Basel). 2023;12(4):833. doi:10.3390/antiox12040833. PMID: 37107208.

19. Mediterranean Diet Reduces Inflammation in Adults: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Nutr Rev. 2026. doi:10.1093/nutrit/nuaf213. PMID: 41211687.

20. Dadkhah Tehrani S, Ramezani Ahmadi A, Sadeghi N, Keshani M. The effects of the Mediterranean diet supplemented with olive oils on pro-inflammatory biomarkers and soluble adhesion molecules: a systematic review and meta-analysis of randomized controlled trials. Nutr Metab (Lond). 2025;22(1):52. doi:10.1186/s12986-025-00947-8.

21. Adherence to the Mediterranean diet can beneficially affect the gut microbiota composition: a systematic review. BMC Med Genomics. 2024;17:83. doi:10.1186/s12920-024-01861-3. PMID: 38632620.

22. Florkowski M, Abiona E, Frank KM, Brichacek AL. Obesity-associated inflammation countered by a Mediterranean diet: the role of gut-derived metabolites. Front Nutr. 2024;11:1392666. doi:10.3389/fnut.2024.1392666.

23. A Low Glycemic Index Mediterranean Diet Combined with Aerobic Physical Activity Rearranges the Gut Microbiota Signature in NAFLD Patients. Nutrients. 2022;14(9):1773. PMID: 35565740.

24. Zelber-Sagi S, Salomone F, Mlynarsky L. The Mediterranean dietary pattern as the diet of choice for non-alcoholic fatty liver disease: Evidence and plausible mechanisms. Liver Int. 2017;37(7):936-949. PMID: 28371239.

25. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis. Gastroenterology. 2015;149(2):367-378. PMID: 25865049.

26. Effect of different exercise modalities on nonalcoholic fatty liver disease: a systematic review and network meta-analysis. Sci Rep. 2024;14:5192. PMID: 38485714.

© 2023 Somato Publications. All rights reserved.