Effects of Mediterranean Diet in Patients with Nonalcoholic Fatty Liver Disease: A Systematic Review, Meta-Analysis, and Meta-Regression Analysis of Randomized Controlled Trials

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Abstract

We conducted a meta-analysis to investigate the effects of the Mediterranean Diet (Med-Diet) on hepatic steatosis and insulin resistance in patients with nonalcoholic fatty liver disease (NAFLD). Six randomized controlled trials were selected for the meta-analysis (sample size: 250 participants). In the meta-analysis, there was no significant difference in body mass index and waist circumference between the Med-Diet and control groups. Med-Diet significantly reduced fatty liver index (FLI) compared with the control diet (standard mean difference [SMD]: −1.06; 95% CI: −1.95 to −0.17; $p = 0.02$). Med-Diet significantly reduced homeostasis model assessment of insulin resistance (HOMA-IR) compared with the control diet (SMD: −0.34; 95% CI: −0.65 to −0.03; $p = 0.03$). Similarly, a meta-regression analysis using age showed that Med-Diet significantly reduced FLI and HOMA-IR (95% CI: −0.956 to −0.237, $p = 0.001$ and 95% CI: −0.713 to −0.003, $p = 0.048$, respectively). This meta-analysis demonstrated that Med-Diet improved hepatic steatosis and insulin resistance in patients with NAFLD. Thus, Med-Diet is a beneficial pharmaconutritional therapy in patients with NAFLD.

Keywords
- Mediterranean diet
- nonalcoholic fatty liver disease
- metabolism
- lipid metabolism
- insulin resistance
- liver stiffness

Nonalcoholic fatty liver disease (NAFLD) is a common metabolic liver disease worldwide and its prevalence is approximately 25% among the general population.[1,2] NAFLD is the leading cause of liver transplantation for women and the second most common for men[3] and is a risk for cardiovascular disease, hepatocellular carcinoma (HCC), and extrahepatic cancers, including colon cancer and breast cancer.[4,5] NAFLD also has a negative impact on patient-reported outcomes, including health-related quality of life.[6] NAFLD is independently associated with a 17% overall excess in healthcare resource utilization and approximately a twofold increase in mortality.[7]

The liver is a major target organ of insulin, and hepatic steatosis causes insulin resistance.[8] Insulin resistance is a feature of metabolic abnormalities in patients with NAFLD[1,9] and is implicated in disease progression from steatosis to nonalcoholic steatohepatitis (NASH).[10] Insulin resistance is also a predisposing factor for cardiovascular diseases.[11] In addition, insulin resistance is a risk factor for advanced hepatic fibrosis and HCC.[8] Since overeating and physical inactivity are significant causative factors for hepatic steatosis and insulin resistance, dietary modifications, and lifestyle interventions are a cornerstone of NAFLD treatment.[1,2]

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The Mediterranean diet (Med-Diet) encompasses traditional eating habits originally developed in the countries bordering the Mediterranean Sea.[12] Med-Diet is characterized by a high intake of plant-based foods and olive oil and low intake of dairy products.[12] Med-Diet has been reported to reduce hepatic fat content and improve insulin resistance in randomized controlled trials (RCTs) in patients with NAFLD.[13,14] However, there are contrasting results, with other studies reporting no effect of the Med-Diet on the improvement of hepatic steatosis[15] and insulin resistance.[16–19] Although Asbaghi et al reported a meta-analysis for the effects of the Med-Diet, the analysis was focused on cardiovascular risk factors such as serum levels of triglyceride and total cholesterol.[4] Thus, the effects of Med-Diet on hepatic steatosis and insulin resistance in patients with NAFLD remain unclear.

The aim of this review is to perform a meta-analysis of RCTs to investigate the effects of Med-Diet on hepatic steatosis and insulin resistance in patients with NAFLD.

Methods

Study Design

This study is designed as a systematic review and meta-analysis of RCTs. This study was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline statement.[20]

Data Sources

A search of the published literature was performed using PubMed, Scopus, and Cochrane Library literature databases up to June 24, 2020.

Search Terms

The following search terms were used to identify potential articles: "non-alcoholic fatty liver disease" OR "non-alcoholic steatohepatitis" OR "nonalcoholic steatohepatitis" OR "fatty liver" OR "steatosis" OR "NAFLD" OR "NASH"; "Mediterranean diet" OR "Mediterranean diets" OR "diets of Mediterranean." The titles and abstracts of studies identified in the search were independently reviewed by three authors (T. K., A. K., and S. Y.) to exclude studies that did not answer the research questions of interest. References within each report that met the selection criteria were manually searched to identify other potentially relevant studies. All relevant abstracts and full-text peer-reviewed articles published in English were collected for analysis.

Inclusion and Exclusion Criteria

Articles were selected if they met the following inclusion criteria: (1) designed as RCT; (2) evaluated the effects of Med-Diet on hepatic steatosis and insulin resistance in patients with NAFLD; (3) included patients with NAFLD diagnosed by liver biopsy, fatty liver index (FLI), or abdominal imaging including ultrasonography and magnetic resonance imaging (MRI). Studies were excluded if they were not RCTs (nonrandomized controlled clinical trials, before and after clinical trials, or observational cohort studies), were not original research (systematic reviews, narrative reviews, commentaries, or editorials), were case reports or conference abstracts, did not report outcomes evaluated in this review, were animal studies, or were not English literature.

Outcomes

Outcomes were body mass index (BMI), waist circumference, FLI, homeostasis model assessment of insulin resistance (HOMA-IR), liver stiffness, and alanine aminotransferase (ALT). Data for each outcome were obtained from original studies. Liver stiffness was evaluated by transient elastography (FibroScan, Echosens, Paris, France)[21] or two-dimensional shear-wave elastography (Aixplorer MultiWave ultrasound system, SuperSonic Imagine S.A., Aix-en-Provence, France).[16]

Data Extraction

Three investigators (T. K., A. K., and S. Y.) individually screened the records and extracted the data. We extracted the following data from each study: first author's name, publication year, study design, study duration, study region, subjects, and characteristics, including age and sex, sample size, method of NAFLD diagnosis, the control diet or intervention, the parameters of the Med-Diet, and mean and standard deviation (SD) of primary outcome measures at the baseline and final stages of the study. All authors agreed upon the studies included and most of the data extracted.

Quality Assessment of the Included Studies

The quality of included studies was independently assessed by two authors (T. K. and A. K.). Randomized controlled studies were assessed by the criteria formulated by the Cochrane Effective Practice and Organization of Care group.[22]

Data Synthesis

The mean and SD of net changes in BMI, waist circumference, ALT, FLI, HOMA-IR, and liver stiffness were calculated for each study. When outcomes were reported as median measures, the median (the first and third quartiles) was converted to mean and SD using the formula in Wan et al's study.[23] For the SD of the change from baseline to end point, we took the correlation coefficient $r = 0.7$ as a conservative estimate.

Statistical Analysis

Meta-Analysis

We employed the standard mean difference (SMD) and 95% confidence intervals (CIs) as a summary statistic.[24] A meta-analysis was performed using Review Manager Software (Review Manager 5.3, Cochrane Collaboration, Oxford, United Kingdom). The random effect model was applied when the test of heterogeneity was $p < 0.10$. Heterogeneity between studies was evaluated by Cochrane's Q test, I^2 index, and t^2 test. In a meta-analysis that showed forest plots with less than four studies, power analysis for meta-analysis was performed as previously described.[25] Publication bias was assessed using visual assessment of funnel plots, Begg test, and Egger's regression asymmetry test. A p-value of <0.05 was considered statistically significant.

Meta-Regression Analysis

An impact of Med-Diet on each outcome was evaluated by a meta-regression analysis with the random effects model using age. Since there was no significant difference in sex among enrolled six studies (risk difference = –0.06; 95% CI: –0.17 to 0.06), sex was not included in the meta-regression analysis in this study. A p-value < 0.05 was considered statistically significant.

Results

Search Results

We identified 428 articles using the prespecified search criteria. Ten additional reports were identified from the article references (►**Fig. 1**). After the removal of duplicates ($n = 178$), a total of 260 articles were screened. We removed 252 articles for the following reasons: basic studies ($n = 117$), review articles ($n = 51$), non-RCTs ($n = 72$), and unrelated research ($n = 12$). A total of eight articles were assessed for eligibility. We removed one article because it lacked a description of the diagnostic tool used to assess steatosis ($n = 1$) and another article because of the Med-Diet arm combined supplementation ($n = 1$). As a result, six articles were included in the qualitative synthesis and meta-analysis[14,16–19,21] (►**Fig. 1**).

Characteristics of Included Studies for Meta-Analysis

All included studies were RCTs conducted between 2013 and 2018 (►**Table 1**). The studies all took place in Western countries. A total of 250 patients with NAFLD were included. The mean age of participants ranged from 33 to 56 years. Study duration ranged from 6 weeks to 6 months. Intervention arms assigned participants to consume the Med-Diet and control arms either provided no intervention or assigned participants to consume other diets such as low-fat diets. The various Med-Diet strategies are described in ►**Table 1**.

Quality Assessment

The quality of the included studies is summarized in ►**Supplementary Table S1**. The quality of RCTs was moderate to high. The major reason for high risk was that participants in the intervention group could not be blinded (in ►**Supplementary Table S1**).

Heterogeneity among the Studies and Power Analysis for Meta-Analysis

The I^2 and t^2 statistics did not show heterogeneity among the studies for analysis of BMI, waist circumference, FLI, and HOMA-IR (►**Figs. 2A, B, 3, and 4**), whereas there was heterogeneity among the studies for analysis of liver stiffness and ALT (►**Fig. 5A, B**).

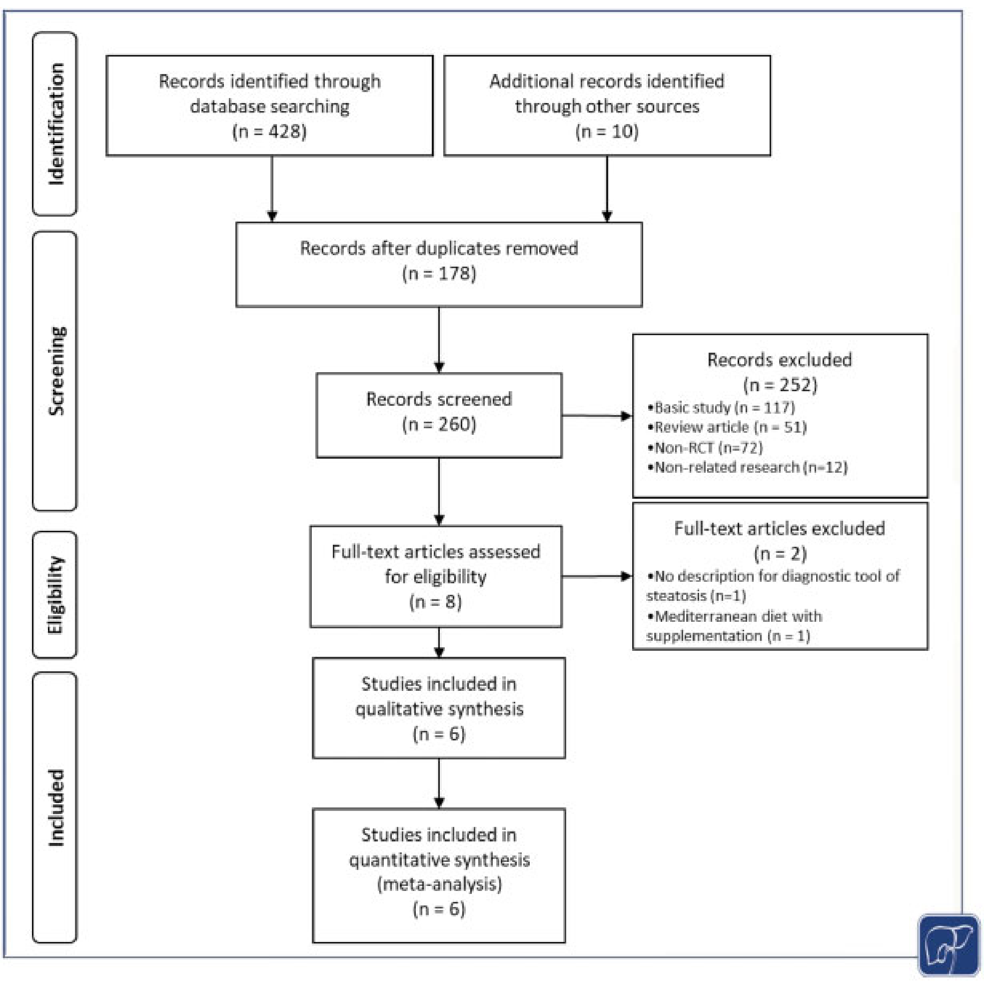

Fig. 1 Flow diagram of studies for inclusion in meta-analysis.

Table 1 Characteristics of included studies

Author	Year	Study design	Study duration	Country	Subjects	Diagnosis of NAFLD	*n*	Age (years)	Sex (female/male)
Abenavoli et al[21]	2017	Randomized controlled trial	6 mo	Italy	NAFLD with obesity	Ultrasonography	Med-Diet: 20 Control: 10	Med-Diet: 52 Control: 33	N/A
Abenavoli et al[18]	2015	Randomized controlled trial	6 mo	Italy	NAFLD with overweight	Ultrasonography	Med-Diet: 10 Control: 10	Med-Diet: 56 Control: 33	N/A
Katsagoni et al[16]	2018	Randomized controlled trial	6 mo	Greece	NAFLD with overweight/obesity	Ultrasonography	Med-Diet: 21 Control: 21	Med-Diet: 44 Control: 47	Med-Diet: 8/13 Control: 8/13
Misciagna et al[19]	2017	Randomized controlled trial	6 months	Italy	NAFLD with diabetes mellitus	Fatty liver index	Med-Diet: 50 Control: 48	N/A	Med-Diet: 16/34 Control: 10/38
Properzi et al[17]	2018	Randomized controlled trial	12 wk	Australia	NAFLD	MRI	Med-Diet: 24 Control: 24	Med-Diet: 51 Control: 53	Med-Diet: 8/16 Control: 11/13
Ryan et al[14]	2013	Randomized crossover controlled trial	6 wk	Australia	Non-diabetic NAFLD	Liver biopsy	Med-Diet/ Control, $n = 12$	Med-Diet/Control 55	Med-Diet/Control 6/6

Control	Med-Diet	Effects of Med-Diet on hepatic steatosis	Effects of Med-Diet on HOMA-IR	Effects of Med-Diet on other metabolic parameters
No pharmacological treatment and lifestyle changes	Low-calorie Med-Diet (1,400–1,600 kcal/day)	A significant reduction of fatty liver index (+7 vs. −19%; $p = 0.017$)	A significant reduction of HOMA-IR value (+46 vs. +6.2%; $p = 0.021$)	A reduction of BMI, waist, hip circumference, and levels of triglyceride and total cholesterol
No pharmacological and/or nutritional treatment	50–60% carbohydrate, 15–20% protein, mono- and polyunsaturated fats (< 30%), saturated fat (< 10%), cholesterol (< 300 mg/day), and fibers (25–30 g/day)	A significant reduction of fatty liver index (+4.6 vs. −28%; $p = 0.009$)	A significant reduction of HOMA-IR value (+51 vs. −6%; $p = 0.043$)	A reduction of BMI, waist circumference, and levels of total cholesterol and triglyceride
45% carbohydrates, 20% protein, and 35% lipid (woman 1500 kcal, man 1800 kcal)	45% carbohydrates, 20% protein, and 35% lipid (women: 1,500 kcal; men: 1,800 kcal).	N/A	No significant difference in changes of HOMA-IR between the two groups	A reduction of BMI and LDL level
Control diet was based on the World Health Organization	A low glycemic index and no more than 10% of total daily calories coming from saturated fats	A significant reduction of fatty liver index (72.69 vs. 57.72; $p < 0.05$)	N/A	
50% carbohydrate, 30% lipid, and 20% protein	40% carbohydrate, 35–40% lipid, and 20% protein	No difference in the reduction of hepatic fat content between the two groups	No significant difference in changes of HOMA-IR between the two groups	A reduction of total cholesterol, serum triglyceride, and HbA1c
30% fat, 50% carbohydrate, 20% protein	40% fat, 40% carbohydrate, and 20% protein	A significant reduction of hepatic steatosis (39 vs. 7%; $p = 0.012$)	A significant reduction of HOMA-IR value (3.9 vs. 3.0; $p < 0.01$)	

Abbreviations: BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; Med-Diet, Mediterranean diet; MRI, magnetic resonance imaging; N/A, not applicable; NAFLD, non-alcoholic fatty liver disease.

In the meta-analysis for FLI and liver stiffness, forest plot showed less than four studies. Power plot analysis the power plot showed 99.8% and 85.1% in the meta-analysis for FLI and liver stiffness, respectively.

Publication Bias

There was no publication bias for BMI, waist circumference, FLI, HOMA-IR, liver stiffness, and ALT (►**Supplementary Fig. S1A–F**) in the funnel plots. The Begg test also showed no publication bias for BMI, waist circumference, FLI, and HOMA-IR, and ALT (►**Supplementary Fig. S1A–D, F**). In Egger's

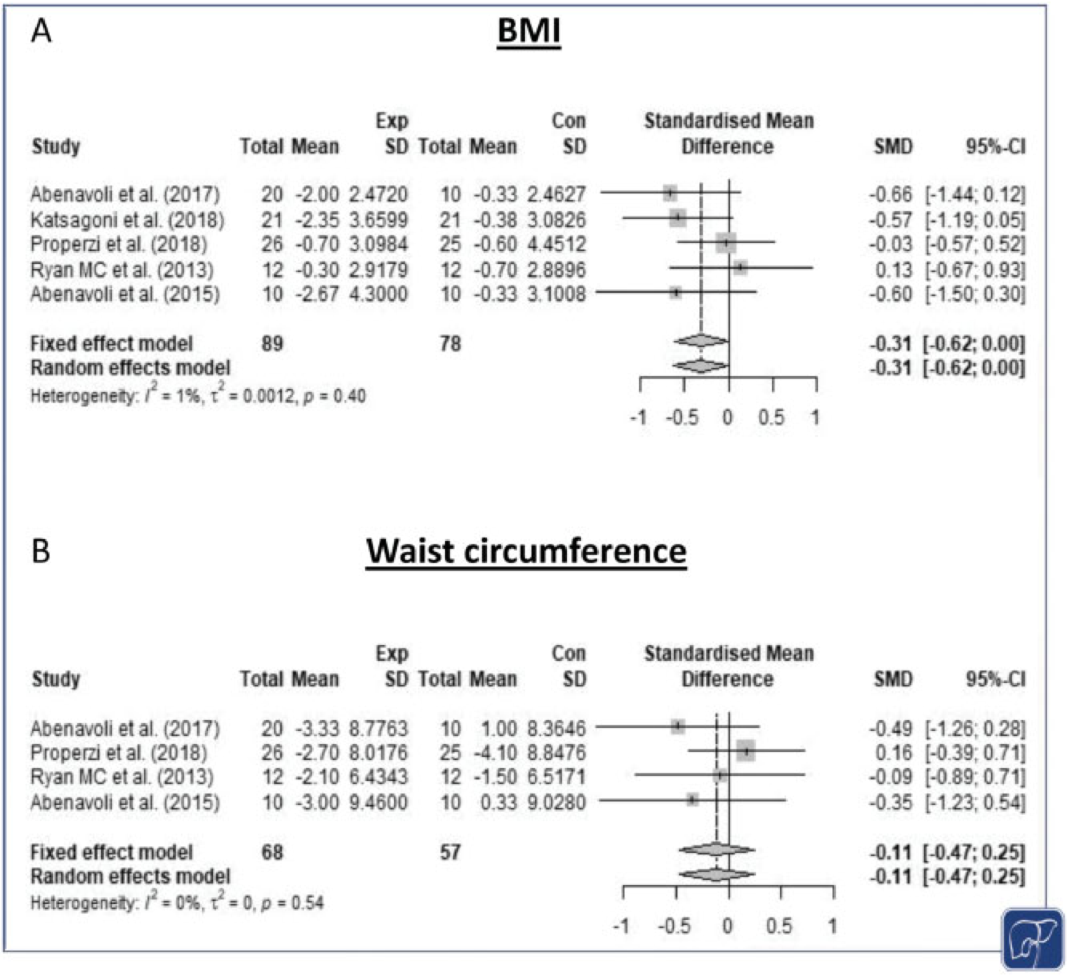

Fig. 2 Forest plot for effect of the Mediterranean Diet on outcomes in patients with nonalcoholic fatty liver disease. (**A**) BMI. (**B**) Waist circumference. CI, confidence interval; BMI, body mass index; SD, standard deviation; SMD, standard mean difference.

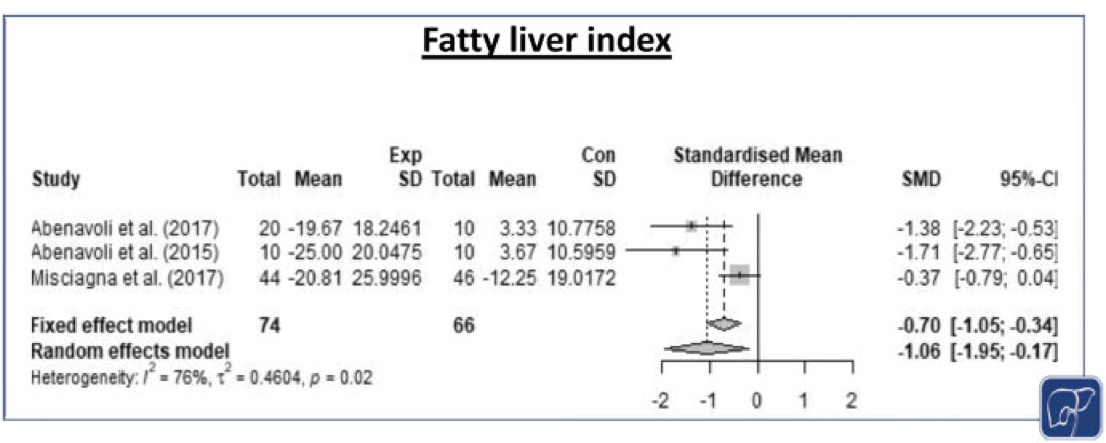

Fig. 3 Forest plot for effect of Mediterranean Diet on fatty liver index in patients with nonalcoholic fatty liver disease. CI, confidence interval; SD, standard deviation; SMD, standard mean difference.

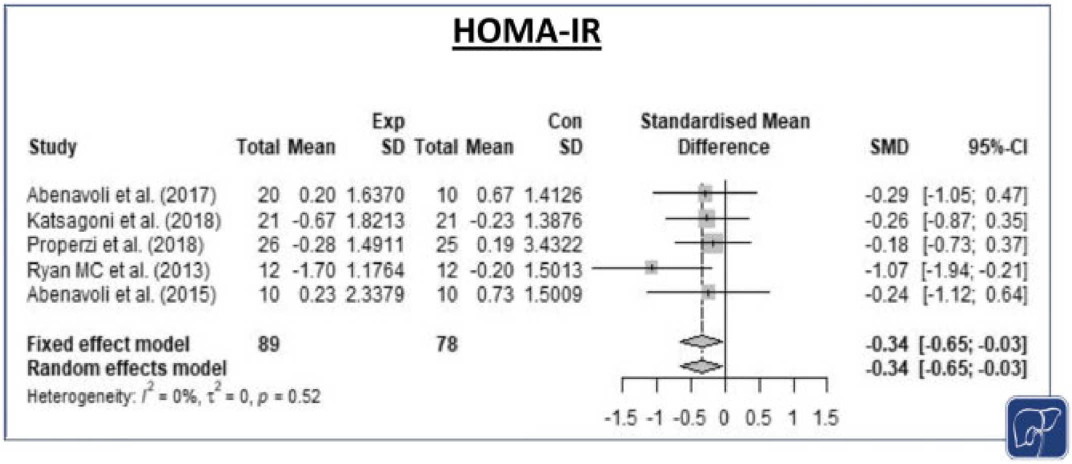

Fig. 4 Forest plot for effect of Mediterranean Diet on HOMA-IR in patients with nonalcoholic fatty liver disease. CI, confidence interval; HOMA-IR, homeostasis model assessment of insulin resistance; SD, standard deviation; SMD, standard mean difference.

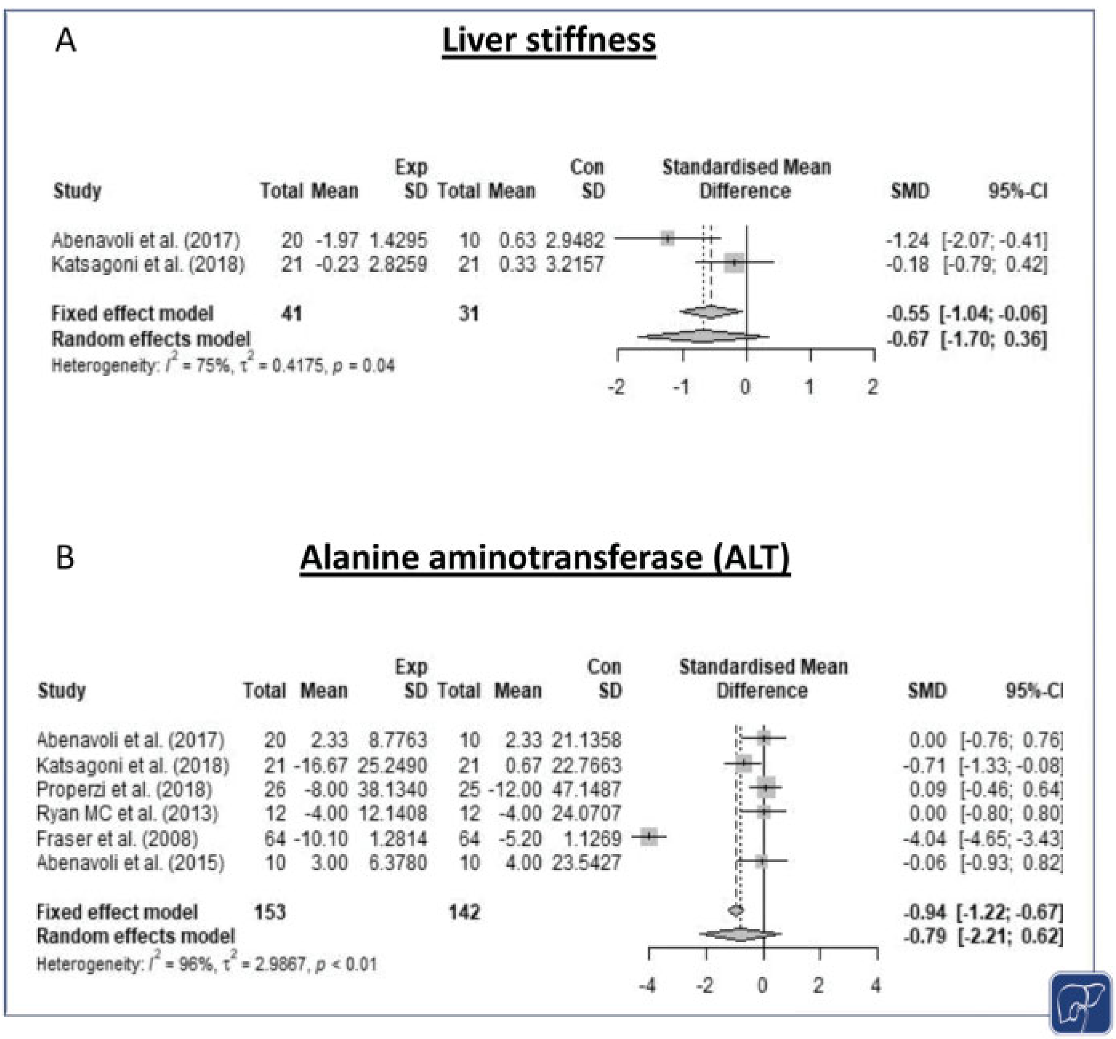

Fig. 5 Forest plot for effect of Mediterranean Diet on (**A**) liver stiffness and (**B**) alanine aminotransferase in patients with nonalcoholic fatty liver disease. Abbreviation: CI, confidence interval; SD, standard deviation; SMD, standard mean difference.

regression asymmetry test, there was a significant bias for FLI. However, there was no publication bias for BMI, waist circumference, HOMA-IR, and ALT (►**Supplementary Fig. S1A–D, F**). The Begg and Egger's regression asymmetry tests were not applicable for liver stiffness due to the small number of studies ($n = 2$) (►**Supplementary Fig. S1F**).

Meta-Analysis for the Effect of Med-Diet on Outcomes in Patients with NAFLD

Body Mass Index

A total of five studies examined the effect of Med-Diet on BMI (►**Fig. 2A**). In the five studies analyzed, four studies showed a reduction of BMI in the Med-Diet group compared with the control group. However, the results were not statistically significant. Overall, there was no significant difference in BMI between the Med-Diet and control groups (SMD: –0.31; 95% CI: –0.62 to 0.00; $p = 0.05$) (►**Fig. 2A**).

Waist Circumference

A total of four studies examined the effect of Med-Diet on waist circumference (►**Fig. 2B**). In the four studies analyzed, three studies showed a reduction in waist circumference in the Med-Diet group compared with the control group. However, the results were not statistically significant. Overall, there was no significant difference in waist circumference between the Med-Diet and control groups (SMD: –0.11 cm; 95% CI: –0.47 to 0.25; $p = 0.55$) (►**Fig. 2B**).

Fatty Liver Index

A total of three studies examined the effect of Med-Diet on FLI (►**Fig. 3**). In the three studies analyzed, all studies showed a reduction of FLI in the Med-Diet group compared with the control group, whereas two studies showed a statistically significant difference. Overall, Med-Diet significantly reduced FLI compared with the control diet (SMD: –1.06; 95% CI: –1.95 to –0.17; $p = 0.019$) (►**Fig. 3**).

Homeostasis Model Assessment of Insulin Resistance

A total of five studies examined the effect of Med-Diet on HOMA-IR (►**Fig. 4**). In the five studies analyzed, all studies showed a reduction of HOMA-IR in the Med-Diet group compared with the control group, and one study showed a statistically significant difference. Overall, Med-Diet showed a statistically significant reduction in HOMA-IR compared with the control diet (SMD: –0.34; 95% CI: –0.65 to –0.03; $p = 0.03$) (►**Fig. 4**).

Liver Stiffness

A total of two studies examined the effect of Med-Diet on liver stiffness (►**Fig. 5A**). In the two studies analyzed, there was a reduction of liver stiffness in the Med-Diet group compared with the control group. However, only one study had statistical significance. Overall, there was no significant difference in liver stiffness between the Med-Diet and control groups (►**Fig. 5A**).

Table 2 Meta-regression analysis with random effects model using age for each outcome

	Estimate	95% CI	*p*-Value
BMI			
Med-Diet	–0.224	–0.562 to 0.113	0.192
Age	–0.349	–0.902 to 0.203	0.215
Waist circumference			
Med-Diet	0.034	–0.379 to 0.448	0.872
Age	–0.404	–0.985 to 0.178	0.173
Fatty liver index			
Med-Diet	–0.596	–0.9557 to –0.2371	0.001
Age	–0.816	–1.3709 to –0.2607	0.003
HOMA-IR			
Med-Diet	–0.358	–0.713 to –0.003	0.048
Age	0.0469	–0.514 to 0.608	0.870
Liver stiffness			
Med-Diet	–0.267	–0.829 to 0.295	0.352
Age	–0.938	–1.852 to –0.023	0.045
ALT			
Med-Diet	–0.187	–0.587 to 0.213	0.360
Age	0.129	–0.485 to 0.744	0.680

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; CI, confidence interval; HOMA-IR, homeostasis model assessment of insulin resistance.

Alanine Aminotransferase

Six studies examined the effect of Med-Diet on ALT (►**Fig. 5B**). In the six studies analyzed, there was a reduction of ALT in the Med-Diet group compared with the control group, but the reduction reached statistical significance in only two studies. Overall, there was no significant difference in ALT between the Med-Diet and control groups (►**Fig. 5B**).

Meta-Regression Analysis

We performed a meta-regression analysis with the random effects model using age for each outcome. Same as the results in the meta-analysis, no significant effects of Med-Diet were seen in BMI, waist circumference, liver stiffness, and ALT. However, Med-Diet significantly reduced FLI and HOMA-IR compared with the control diet in the meta-regression analysis (►**Table 2**).

Discussion

Lifestyle changes, including nutrition, are a core component of the management of NAFLD and NASH. In this study, we conducted a meta-analysis and a meta-regression analysis of six RCTs to determine the impact of adherence to the Med-Diet, a common dietary recommendation in patients with NAFLD, on parameters relevant to outcomes. The main finding of this analysis is that FLI and HOMA-IR values are significantly improved by the Med-Diet. In contrast, BMI, waist circumference, and ALT were not improved. Because hepatic steatosis and insulin resistance are associated with cardiovascular disease and cancers, such as HCC, colorectal cancer, and breast cancer, the Med-Diet may be a beneficial pharmaconutritional therapy for patients with NAFLD by reducing disease activity and the incidence of comorbidities.

In both meta-analysis and meta-regression analysis, there was no significant difference in BMI and waist circumference between the Med-Diet and control groups. While BMI and waist circumference reduction are basic therapeutic goals for patients with NAFLD,[1,9] glucose and lipid regulation, regardless of anthropometric changes, are important factors in the pathogenesis of NAFLD.[26] The Med-Diet has been reported to modulate these factors.[27] Specifically, the consumption of extra virgin olive oil and lower carbohydrate content was shown to reduce hepatic fat content in the PREDIMED (Prevención con Dieta Mediterránea)[26] and CENTRAL (Diet and Body Composition) trials,[13] respectively. The Med-Diet contains high levels of α-linolenic acids and polyphenols, which have been shown to attenuate hepatic steatosis through downregulation of transcription factors implicated in adipogenesis and lipogenesis, including the peroxisome proliferator-activated receptor[28] and the carbohydrate response element binding protein.[29,30] In both meta-analysis and meta-regression analysis, the Med-Diet led to significant reductions in the FLI. Thus, the Med-Diet can improve hepatic steatosis independently of a significant reduction in body weight or visceral fat.

FLI is a biomarker developed to predict the existence of hepatic fat.[31] FLI may be influenced by inflammation and fibrosis[32] and has been associated independently with liver-related mortality.[33] The FLI is also known to have an association with higher incidences of comorbidities in patients with NAFLD, including cardiovascular disease,[34] colorectal cancer,[35] and breast cancer.[36] Calori et al demonstrated that these associations appear to be tightly interconnected with the risk conferred by the correlated insulin-resistant state in a large population-based cohort from Cremona in Northern Italy over a 15-year period.[33] Med-Diet has been reported to reduce the risk of cardiovascular diseases, colorectal cancer, and breast cancer,[37] although the mechanisms for the mitigation of these comorbidities remain unclear. These meta-analysis and meta-regression analysis demonstrated that the Med-Diet groups had a significant reduction in HOMA-IR compared with the control group. The results were consistent with those of a previous meta-analysis by Asbaghi et al.[38] Med-Diet contains various functional nutrients, including extra virgin olive oil, polyunsaturated fatty acids, and anthocyanins that are reported to improve insulin resistance in animal studies.[39] Insulin resistance increases the risk of life-threatening events including cardiovascular disease and HCC in patients with NAFLD.[40,41] A meta-analysis demonstrated that the Med-Diet is associated with improved glycemic control and decreased cardiovascular risk among subjects with type 2 diabetes mellitus in comparison to controls.[42] Higher adherence to the Med-Diet is additionally associated with the prevention of HCC.[43] This is perhaps due to the action of insulin resistance as an independent risk factor for advanced hepatic fibrosis in patients with NAFLD.[44] Thus, the Med-Diet may possibly improve the prognosis of patients with NAFLD by reducing insulin resistance.

Although this meta-analysis showed improvement in insulin resistance among groups adherent to the Med-Diet, it did not show a significant reduction in liver stiffness. Only two included RCTs investigated changes in liver stiffness, and the small sample size may limit the ability to demonstrate this outcome. Similar limitations apply to changes in ALT, with ALT elevations not required for study entry, making changes in ALT difficult to detect. Additionally, the trials spanned at most 6 months. It is likely that notable changes in the degree of fibrosis may develop over a longer period. This analysis does not exclude the possible benefits of the Med-Diet on liver stiffness or ALT. Lastly, this meta-analysis did not assess all factors, including genetics, dyslipidemia, hypertension, and insulin resistance, that underlie the pathogenesis of hepatic fibrosis in patients with NAFLD.[44,45] Regardless, the reduction in insulin resistance demonstrated by these meta-analysis and meta-regression analysis is an important finding. A recent study also reported that the Med-Diet is associated with lower NAFLD fibrosis scores and fibrosis-4 indices in patients with type 2 diabetes mellitus and insulin resistance.[46] Thus, Med-Diet may in particular decrease insulin resistance-related hepatic fibrosis.

There are several limitations to this study. First, there was heterogeneity regarding the diagnosis of NAFLD. Different methods are used for its diagnosis in different RCTs. Second, no study evaluated the effect of the Med-Diet on parameters related to NAFLD pathogenesis beyond 6 months. Third, only a small number of RCTs are included. Only two RCTs investigate the effect of the Med-Diet on hepatic fibrosis, which is an important prognostic factor for patients with NAFLD. Fourth, there was heterogeneity among participants due to comorbidities. For example, some trials included patients with NAFLD without diabetes and others included patients with NAFLD and diabetes or NAFLD and obesity. Thus, there is a need for larger RCTs that assess the long-term effect of the Med-Diet on hepatic fibrosis in patients with NAFLD diagnosed by the same criteria.

Conclusion

We performed a meta-analysis and a meta-regression analysis of six RCTs that demonstrate the beneficial effects of Med-Diet adherence on FLI and HOMA-IR values in patients with NAFLD. This review demonstrates that a low-cost intervention such as dietary counseling in the outpatient clinic setting can effectively regulate glucose and lipid metabolism pathways that are implicated in the progression of NAFLD severity and the development of significant comorbidities.

Main Concepts and Learning Points

- The Med-Diet has been reported to improve metabolic abnormalities in patients with NAFLD. However, the reported effects have been inconsistent in RCTs.

- This meta-analysis demonstrated that the Med-Diet improved hepatic steatosis and insulin resistance in patients with NAFLD.
- The Med-Diet is a beneficial pharmaconutritional therapy in patients with NAFLD.

Authors' Contributions

T. K. and M. C. participated in study conception and design. T. K., A. K., and S. Y. participated in data search and data extraction. T. K. and A. K. participated in the quality assessment of the studies. T. K. and A. K. participated in the analysis. D. N., T. T., M. Z., and T. T. participated in the acquisition of data and interpretation of data. T. K., S. Y., D. N., M. Z., and T. T. participated in the drafting of the manuscript. M. C. and T. T. participated in critical revision.

Disclosure

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Conflict of Interest

The other authors have no conflicts of interest relevant to this publication.

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