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Meta-analyses

Critical appraisal for low-carbohydrate diet in nonalcoholic fatty liver disease: Review and meta-analyses

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SUMMARY

Background & aims: Weight loss by lifestyle modification is the cornerstone therapy of Non Alcoholic Fatty Liver Disease. Low carbohydrate diet has showed favorable effects for body weight as well as hepatic fat content in several reports. In this meta-analysis, we review clinical studies article to date regarding the composition of the diet and analyzed the impact of low carbohydrate diet comparing to low calorie diet on hepatic fat change, AST and ALT using Forest plot. We aimed to investigate the efficacy of low carbohydrate diet on NAFLD.
Methods: We collected studies that were conducted with various amounts of carbohydrate and different methods for changing the hepatic fat and fibrosis.
Results: Eleven clinical studies (seven randomized controlled trials) were selected on the efficacy and safety of low carbohydrate diet on NAFLD patients. Four studies evaluated hepatic fat by magnetic resonance imaging and two evaluated hepatic fat using computed tomography. However, the pools of subjects were small, the criterion for low carbohydrate was variable, and there is yet an established standard method of evaluation of liver. In meta-analysis, there was no significant difference between low carbohydrate diet group and low fat diet group on the improvement of hepatic fat content and transaminases in NAFLD.
Conclusion: So far there's little evidence that low-carbohydrate diet has more beneficial effect on NAFLD than low calorie diet in similar calorie intake.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is very closely associated with obesity and dietary habits. There is no effective drug yet for NAFLD, and weight reduction through diet modification is the cornerstone of treatment [1]. Carbohydrates are known to play an important role in the synthesis of intrahepatic fat and in whole-body insulin resistance [2]. Degree of hepatic inflammation showed positive correlation with amount of carbohydrate energy intake percent in cross-sectional studies [3,4]. Overconsumption of fructose and saturated fat is also associated with NAFLD. Lifestyle changes with healthy diet and physical activity have been recommended as the primary therapy for management of NAFLD in lots of convincing studies [5]. There is a growing interest in the low-carbohydrate high-fat diet in NAFLD patients [6]. Several reports suggested beneficial effects of low-carbohydrate high fat diet on fatty liver disease as well as obesity. There is also an ongoing debate about its long-term safety in association with cardiovascular disease [7,8]. However, clinical studies available to date regarding the composition of diet in NAFLD have different outcomes and are few in number. The prior meta-analysis on the low carbohydrate diet in NAFLD didn't compare hepatic fat reduction and transaminase improvements to low fat diet and the meta-analysis were conducted on the changes in intrahepatic fat mass and liver enzyme chemistry before and after the low-carbohydrate diet [9]. Most studies that were in the previous meta-analysis showed decrease in

Abbreviation: NAFLD, nonalcoholic fatty liver disease; RCT, randomized controlled trial; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IHTG, intrahepatic triglyceride; CHO, carbohydrate; MRS, magnetic resonance spectroscopy; Cal, calories; n.s., not significant; carb, carbohydrate; Low carb, Low-carbohydrate diet group; Low fat, low fat diet group.

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liver fat content as well as weight loss after low carbohydrate diet. It is hard to discriminate whether that beneficial effect on NAFLD came from weight loss itself or modulation of macronutrient composition. The carbohydrate ratios of studies were not mentioned in this meta-analysis. They also administered other components of intervention such as reducing fructose, the Mediterranean diet and physical activity which were excluded from our study. Therefore, it is still unclear whether these beneficial effects of low carbohydrate diet are independent of calorie intake and body weight change.

In this meta-analysis, we analyzed the impact of low carbohydrate diet compared to low calorie diet on hepatic fat change, AST and ALT using forest plot and reviewed the selected studies with respect to the method of hepatic function, the ratio of carbohydrate intake and study duration. We investigate the efficacy and safety of the low-carbohydrate high-fat diet in patients with NAFLD.

2. Methods

We searched MEDLINE (January 1, 1976 to May 30, 2017) and EMBASE (January 1, 1985 to May 30, 2017) with no restriction on language or year of publication. The following keywords and MeSH were included: carbohydrate-restricted diet, dietary carbohydrates/pharmacology, caloric restriction, steatohepatitis, fatty liver, hepatic fat, non-alcoholic fatty liver disease, liver/metabolism and liver/pathology. In the search strategies, we adapted the MEDLINE strategy. The further relevant articles were manually searched from the references of related articles.

2.1. Study selection

Two reviewers (J. Ahn, D.W. Jun) independently decided the inclusion of all studies based on the selection criteria. The flow chart for our literature identification is shown in Fig. 1. A total of 441 records were identified. 42 duplicated studies removed. 397 records were screened based on titles and abstract at first. Of these, 372 studies were discarded as it was clearly irrelevant to the selection criteria. For the remaining 27 articles, we screened the full text. Studies were included in our review if they [1] were conducted in NAFLD patient or high risk NAFLD patient [2], performed the restricted carbohydrate diet program with no supplement intake [3]. result with a measured hepatic outcome such as hepatic fat content, histology, serum ALT, AST and [4] were written in English. We excluded studies on the pediatric patients. We selected randomized controlled study, comparative studies and case control studies and excluded reviews, cross-sectional articles and case−control studies less than 5 subjects. Disagreements were resolved by discussion or by consulting the third author.

2.2. Data extraction

Data from eligible studies were extracted by the two reviewers independently. Any discrepancy was resolved by consensus. The following variables were extracted from studies [1]: Mean and SD of carbohydrate, fat, and total calorie intake, hepatic fat contents, AST and ALT before and after intervention [2] the duration of diet program, other dietary details (ex. ad libitum) [3], characteristic of subjects (weight, BMI, selection criteria, the method of diagnosis on NAFLD). When the amount of macronutrient intake provided with g/day, we transformed the figures into percentage of total calorie intake.

2.3. Statistical analysis

The main outcome of our review is the changes of hepatic fat contents and aminotransferase activity after low carbohydrate diet. These estimates were expressed in terms of standardized mean difference and standard errors. Random effect model with an inverse variance method was used to calculate the standard mean differences displaying 95% confidence intervals between the low carbohydrate diet group and low fat diet group. For assessing heterogeneity between studies, we used the I^2 statistic. The heterogeneity was considered low, moderate, and high with values of 25%, 50%, 75% respectively. P value less than 0.05 considered statistically significant. We used RevMan version 5.3 for these analyses.

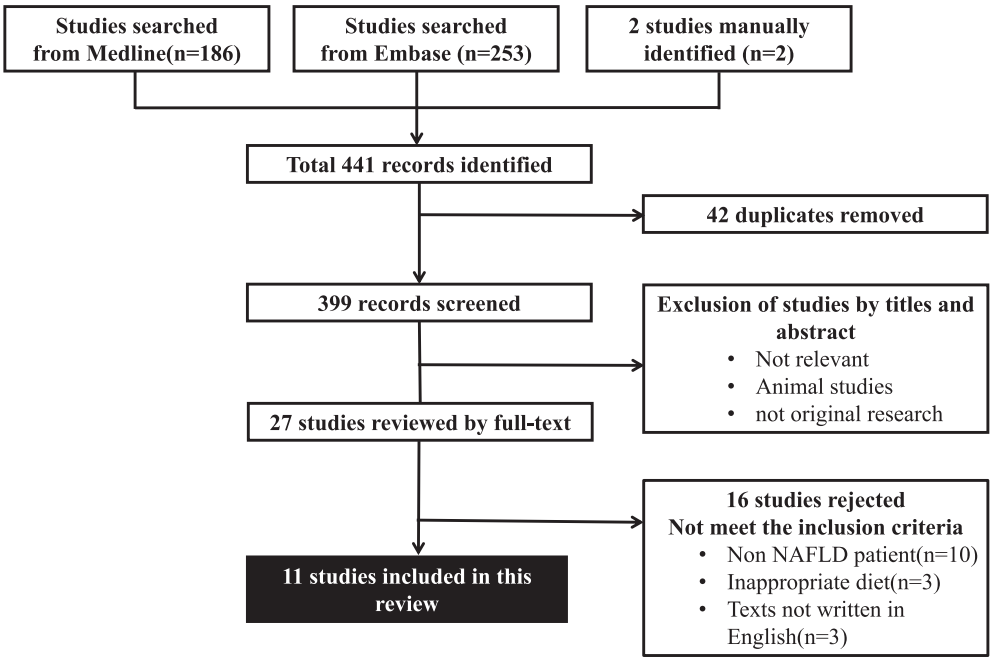

Fig. 1. Flow chart of study selection.

3. Results

3.1. Definition and type of low-carbohydrate diet

There is a lack of consensus on the definition of the low-carbohydrate diet; however, it can generally be classified into three categories depending on the amount of carbohydrate intake [10,11]. First, the "moderate carbohydrate diet" or "reduced carbohydrate diet" could be defined as a ratio of carbohydrate intake to the total calorie intake per day of between 26% and 45%, or >130 g/day. Next, when the carbohydrate intake ratio is <26%, or >30 g/day, it is classified as a "low-carbohydrate diet." When the carbohydrate intake rate is <10%, or <30 g/day, it can be categorized as the "ketogenic diet" or a "very-low-carbohydrate diet" (Fig. 2). As the ratio of carbohydrate intake decreases, the proportion of fat increases. In fact, a very-low-carbohydrate diet is almost synonymous to a very-high-fat diet.

3.2. Overview of low-carbohydrate diet in NAFLD

MEDLINE, and EMBASE (January 1, 2000 to May 30, 2017) with English publication. All clinical trials which primary endpoint was changes of hepatic steatosis or aminotransferase activity using low carbohydrate diet program were included. A total of 11 intervention studies have been conducted on the effects of a low-carbohydrate diet in NAFLD (Table 1) [2,12–21]. Most studies compared the efficacy of a low-carbohydrate high-fat diet with that of a high-carbohydrate low-fat diet. Eight studies were conducted in Western countries and three trials were performed in Asia [12,16,17]. Only one study used liver biopsy; four studies performed liver magnetic resonance imaging; and four studies compared the changes of liver enzymes as the primary end point. According to carbohydrate intake, these 11 studies can be divided into three groups: 5 studies on the reduced carbohydrate diet (<26%–45%), 2 studies on the low-carbohydrate diet (<10%–25%), and 4 studies on the very-low-carbohydrate diet (<10%). Six studies measured the changes in intrahepatic fat [12–15,18]. The serum liver enzyme concentration was also evaluated as the primary endpoint in four studies.

3.3. Hepatic fat changes in low-carbohydrate diet

Five research papers compared the intrahepatic fat changes using H-MRS and CT before and after interventions with a low-carbohydrate diet and a low-fat diet (Table 2) [13–15,18]. In the randomized controlled studies using H-MRS, there was no significant difference in intrahepatic fat reduction between low carbohydrate diet and low fat diet (RR = 95% C.I.: 1.39 (−0.25 − 3.02), I^2 = 91%, Fig. 3). High heterogeneity was observed. Browning et al. [14] randomly assigned patients with NAFLD to a low-carbohydrate diet group (carbohydrate intake <20 g/day, no limit on calorie intake) and a low-calorie diet group (1200 kcal for women, 1500 kcal for men) for 2 weeks. The weight loss between the two groups was similar; however, intrahepatic fat was significantly reduced in the low-carbohydrate group (−55% ± 14 vs. −28.0% ± 23, P = 0.008). Kirk et al. [18] conducted a randomized controlled study in 22 obese patients including 12 with NAFLD who had reduced their carbohydrate intake to <10% and were evaluated for liver fat mass 48 h and 6 weeks (mean 6 ± 1 weeks) later. After 48 h, patients with a low-carbohydrate diet showed a faster reduction of intrahepatic fat mass than those with a high-carbohydrate diet (29.6% ± 4.8 vs. 8.9% ± 1.4, P < 0.05); however, there was no difference between the two diet groups after 6 weeks. Haufe et al. [15] randomized 102 obese patients including 46 with NAFLD into a low-carbohydrate diet group (carbohydrate 25%, fat 45%, 1600 kcal/day) and a low-fat diet group (carbohydrate 52%, fat 27%, 1600 kcal/day). Their comparative study found no significant difference in intrahepatic fat reduction between the two groups. Jang et al. [16] randomized 110 NAFLD into a low-carbohydrate and low-fat education group. Intrahepatic fat amount assessing by CT was more decrease in low-carbohydrate group than low-fat education group, but total energy intake was also further decreased in the low-carbohydrate group compared to the low-fat group. Calorie restriction rather than type of macro-nutrition composition is risk factor in improving fatty liver. Bian et al. [13] measured the liver volume and intrahepatic fat before and after the intervention. One group with 17 patients with NAFLD had restricted carbohydrate intake to <20 g for 6 days. The other group with 26 patients with NAFLD had a total calorie consumption of up to 1000 kcal/day for 7 months. In the end, there was no significant difference in intrahepatic fat between the two groups.

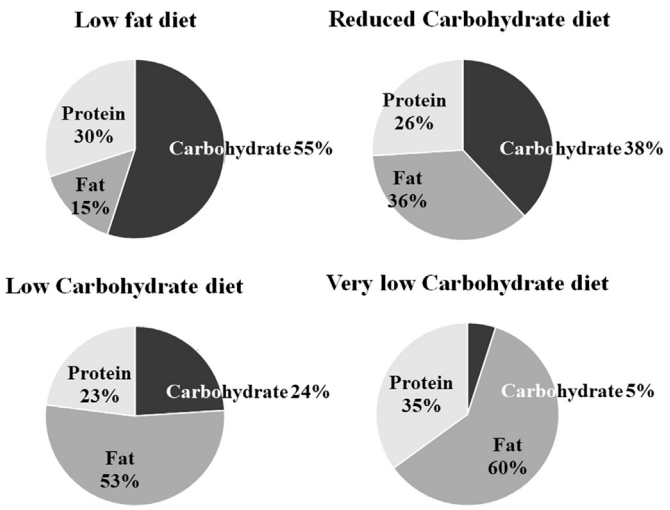

Fig. 2. The classification of low carbohydrate diet.

3.4. Histopathological changes in low-carbohydrate diet

Only one study performed liver biopsy to examine hepatic steatosis, inflammation, and fibrosis before and after an intervention with a low-carbohydrate diet. Tendler et al. [21] assigned five patients with NAFLD to a very-low-carbohydrate diet, in which the patients consumed <20 g/day of carbohydrate for 6 months. The average weight loss was 12.8 kg, and steatosis, inflammation, and fibrosis grade were improved in four of the five patients (Table 3). In one patient who did not adhere to the proposed dietary program, the grade of NAFLD severity on biopsy was increased.

3.5. Biochemical changes in low-carbohydrate diet

Seven interventional studies evaluated the effects of the low-carbohydrate diet and the low-fat diet on ALT/AST changes in patients with NAFLD (Table 4) [2,14,15,17–20]. All studies were randomized controlled trials (RCTs). However, NAFLD was diagnosed on the basis of clinical parameters, and none of the studies conducted liver biopsy. Regarding the improvement on ALT and AST, there was no significant difference between two type of diets. (ALT, RR: 95% C.I.: = 0.5 (−0.13- 1.14), I^2 = 73%, Fig. 4) (AST, RR: 95% C.I. = 0.61 (−0.18- 1.40), I^2 = 77%, Fig. 5). Two reports which did not showed numerical results excluded in Forest plot [15,20]. ALT/AST improvements were observed in two studies on the low-carbohydrate diet and in one study on the low-fat diet. However, ALT/AST showed no significant difference between the two

Table 1
Characteristics of trials studying the effects of carbohydrate ratio on NAFLD.

First author, year	Subject, country	Diagnosis Method	Design	Intervention	Control	Duration	Outcome	Conclusion
Randomized controlled trial (RCT)								
Browning [14], 2011	18 NAFLD, United States	Liver Biopsy	RCT	CHO 8%, fat 59%, protein 33%, energy 1553 kcal/day, no limit on calorie intake	CHO 50%, fat 34%, protein 16%, energy 1325 kcal/day	2 weeks	MRS	IHTG showed greater decreases in low-CHO diet.
Kirk [18], 2010	22 obese, United States	MRS	RCT	CHO 10%, fat 75%, protein 15%, ~1100 kcal/day energy	CHO 65%, fat 20%, protein 15%, ~1100 kcal/day energy	48 h, and 6 weeks	MRS	IHTG decreases in low-CHO at 48 h; no difference at 6 weeks.
Haufe [15], 2011	102 obese, Germany	MRS	RCT	CHO 100–110 g (25%), fat 70–80 g/day (45%), energy 1600 kcal/day	CHO 200–230 g (52%), fat 40–60 g (27%), energy 1700 kcal/day	6 months	MRS	IHTG and AST were not different in both diets.
Jang [16]	110 NAFLD, Korean	CT	RCT	CHO 243 g, fat 42.7 g, energy 1648 kcal/day	CHO 264 g, fat 48.3 g, energy 1787 kcal/day	2 months	CT	Total calorie and hepatic fat decreased more in low-CHO diet program
de Luis [2], 2010	30 NAFLD, Spain	BMI>30 ALT>43	RCT	CHO 38%, fat 36%, protein 26%, energy 1507 kcal/day	CHO 53%, fat 27%, protein 20%, energy 1500 kcal/day	3 months	Chemistry	ALT and AST decreased more in the low-fat diet
Kani [17], 2014	30 NAFLD, Iran	Ultrasonography	RCT	CHO 45%, fat 35%, protein 20%, energy 2091 kcal/day	CHO 55%, fat 30%, protein 15%, energy 2048 kcal/day	8 weeks	Chemistry	AST decreased more in the low-CHO diet
Ryan [20], 2007	52 obese, United States	MRS	RCT	CHO 42%, fat 39%, protein 18%, energy 1595 kcal/day	CHO 58%, fat 23%, protein 18%, energy 1699 kcal/day	16 weeks	Chemistry	ALT decreased more in the low-CHO diet
Non randomized controlled trial								
Rodriguez-Hernandez [19], 2011	54 NAFLD, Mexico	Ultrasonography	Randomized, not controlled	CHO 45%, fat 28%, protein 27%, energy 1593 kcal/day	CHO 54%, fat 21%, protein 25%, energy 1593 kcal/day	6 months	Chemistry	ALT and AST decreased more in the low-CHO diet but not significantly.
Bian [13], 2014	43 NAFLD, Finland	MRS	Comparative, double arm	CHO <20 g/day, 1000 kcal/day energy deficit	CHO 50%, fat 30%, protein 20%, 1000 kcal/week deficit until 5% weight loss		MRS	Liver fat decreased similarly in both diets.
Benjainov [12], 2007	14 Obese, Israel	CT	Single arm	CHO 14%, fat 56%, protein 29%, energy 1520 kcal/day , no limit on calorie intake		4 weeks	CT	Low-CHO diet reduced liver fat content and size.
Tendler [21], 2007	5 NAFLD, United States	Liver biopsy	Single arm	CHO <20 g/day, no limit on calorie intake		6 months	Liver biopsy	Low-CHO diet improved steatosis, inflammation, and fibrosis

NAFLD, nonalcoholic fatty liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IHTG, intrahepatic triglyceride; CHO, carbohydrate; MRS, magnetic resonance spectroscopy.

groups in the remaining four studies. In the study with the longest study period of 6 months, the carbohydrate ratio did not affect the AST and ALT levels. de Luis et al. [2] showed both AST and ALT levels were significantly reduced in the low-fat diet group. Ryan et al. [20] found that the ALT levels were only significantly improved in the low-carbohydrate diet group (−9.5 vs. −4.2 U/L, $P < 0.04$). Kani et al. [17] also conducted an RCT for 2 months in 30 patients with NAFLD. As a result, only AST levels were significantly decreased in the low-carbohydrate diet group (−5.9 vs. −3.0, $P < 0.05$). In the remaining four RCTs, the decrease in both AST and

Table 2
Intrahepatic fat reduction in various low-carbohydrate diets.

First author, year	Low CHO		Low fat		Hepatic fat change %				Outcome measurement tool	Remark
	CHO %	Cal (kcal)	CHO %	Cal (kcal)	Low CHO	Low fat	*P* value	Ratio		
Browning [14], 2011	8%	1553	50%	1325	55%↓	8%↓	0.008	6.87	MRS	*Ad libitum* on low CHO
Kirk [18], 2010	10%	1100	65%	1100	29.6%↓	8.9%↓	<0.05	3.32	MRS	48 h
Kirk [18], 2010	10%	1100	65%	1100	38%↓	44.5%↓	n.s.	0.85	MRS	6 weeks
Bian [13], 2014	10%	1000	50%	1000	24.3%↓	27.7%↓	n.s.	0.87	MRS	
Haufe [15], 2011	25%	1600	52%	1700	50.0%↓	44.2%↓	n.s.	1.12	MRS	*Ad libitum* on low CHO
Jang [16], 2017	59%	1648	59%	1787	4.0%↓	2.6%↓	<0.05	1.53	CT	CHO% was similar

Abbreviations: CHO, carbohydrate; Cal, calories; MRS, magnetic resonance spectroscopy; n.s., not significant.

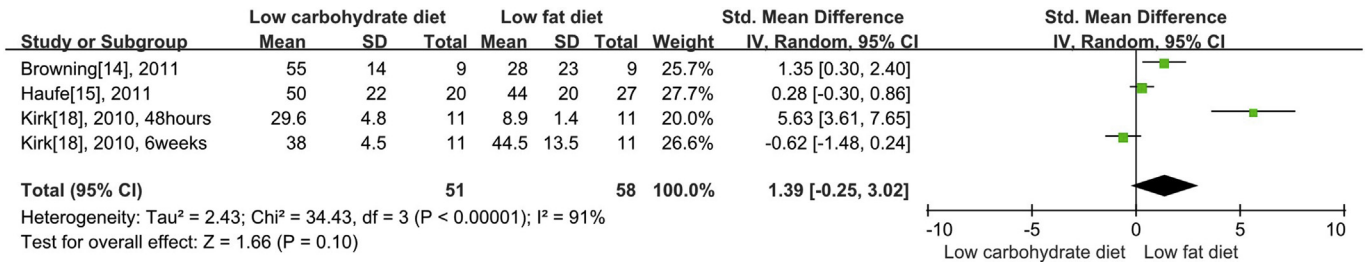

Fig. 3. Forest plot of % change in hepatic fat content by low carbohydrate diet and low fat diet in NAFLD patient.

Table 3
Intrahepatic inflammation and fibrosis in various low-carbohydrate diets.

First author, year	Study design	n	Intervention	Steatosis	Inflammation	Fibrosis
Tendler [21], 2007	Single-arm study	5	CHO intake <20 g/day, no limit on calorie intake, 6 months	4 of 5 improved	4 of 5 improved, 3 of 5 completely recovered	4 of 5 improved, 3 of 5 completely recovered

Abbreviation: CHO, carbohydrate.

Table 4
Biochemical changes in various low-carbohydrate diets.

First author, year	Low carb group CHO %	Low fat group CHO %	Duration	ALT	AST
Kirk [18], 2010	10%	65%	48 h	Same	Same
Browning [14], 2011	8%	50%	2 weeks	Same	Same
Kirk [18], 2010	10%	65%	6 weeks	Same	Same
Kani [17], 2014	45%	55%	2 months	Same	↓ Low carb
de Luis [2], 2010	38%	53%	3 months	↓ Low fat	↓ Low fat
Ryan [20], 2007	42%	58%	4 months	↓ Low carb	Not mentioned
Rodriguez-Hernandez [19], 2011	45%	54%	6 months	Same	Same
Haufe [15], 2011	25%	52%	6 months	Same	Not mentioned

Abbreviations: carb, carbohydrate; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

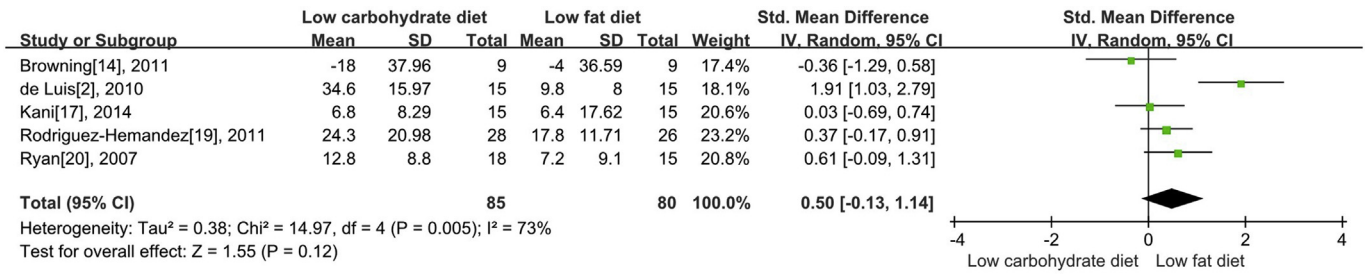

Fig. 4. Forest plot of ALT decrement by low carbohydrate diet and low fat diet in NAFLD patient.

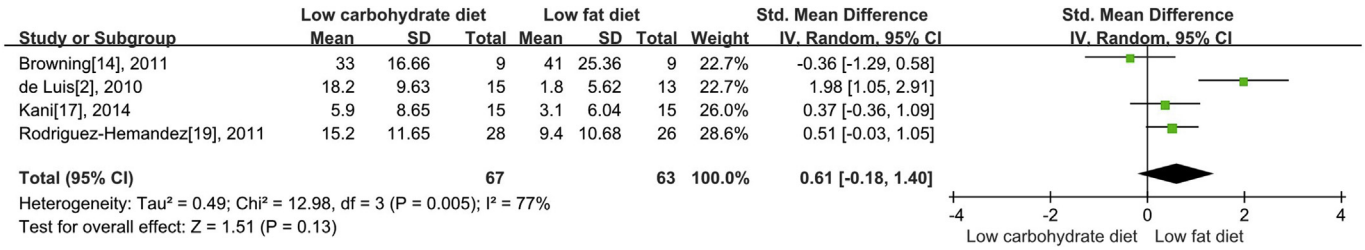

Fig. 5. Forest plot of AST decrement by low carbohydrate diet and low fat diet in NAFLD patient.

Table 5
Clinical outcomes according to carbohydrate energy percentage.

First author, year	Low carb	Low fat	Duration	MRS	ALT	AST
Browning [14], 2011	8%	50%	2 weeks	**Favorable to carb**	Same	**Same**
Kirk [18], 2010	10%	65%	48 h	**Favorable to carb**	Same	Same
Kirk [18], 2010	10%	65%	6 weeks	Same	Same	Same
Bian [13], 2014	10%	50%	6 days/7 months (low carb/low fat)	Same	Same	Same
Haufe [15], 2011	25%	52%	6 months	Same	Same	Not mentioned
de Luis [2], 2010	38%	53%	3 months		Favorable to fat	Favorable to fat
Ryan [20], 2007	42%	58%	4 months		**Favorable to carb**	Not mentioned
Kani [17], 2014	45%	55%	2 months		Same	**Favorable to carb**
Rodriguez-Hernandez [19], 2011	45%	54%	6 months		Same	Same

Abbreviations: carb, carbohydrate; MRS, magnetic resonance spectroscopy; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

ALT concentrations was not statistically significant in the two diets [14,15,18,19].

3.6. Optimal "Cutoff" of carbohydrate intake

We compared the efficacy according to degree of carbohydrate restriction (Table 5). Studies on very-low-carbohydrate diets (<10% carbohydrate), low-carbohydrate diet (<26% of the daily carbohydrate ratio), and reduced carbohydrate diets (<45% carbohydrate) showed various results [13,14,18]. There was no correlation between the degree of carbohydrate restriction and the improvement of NAFLD.

3.7. Optimal duration of low-carbohydrate diet

The results of five trials that measured intrahepatic fat mass with MRS showed that the longer the intervention period, the better the reduction in intrahepatic fat mass (Fig. 6) [13–15,18]. A short-term low-carbohydrate diet reduced intrahepatic fat in the range of 20%–60% within 2 weeks, whereas two long-term interventional studies showed reduction in intrahepatic fat in the range of 38.9%–50%. A low-fat diet within 2 weeks of intervention reduced intrahepatic fat loss by <10%, and two studies with relatively long intervention periods showed a >40% hepatic fat reduction but no significant difference in intrahepatic fat loss compared with the low-carbohydrate diet. However, only one study [15] maintained the low-carbohydrate diet for >6 months, whereas all the others had a study period of <8 weeks. The low-carbohydrate diet group showed faster weight loss than the low-fat diet group; however, in the end, there was no difference between the two groups [15]. The decrease in intrahepatic fat was also effective initially in the low carbohydrate diet group; however, it seemed that the longer the intervention period, the less the difference in fat loss between the two dietary therapies [18]. Intrahepatic fat mass may also have a pattern similar to that of weight loss; however, more RCTs are needed to compare them.

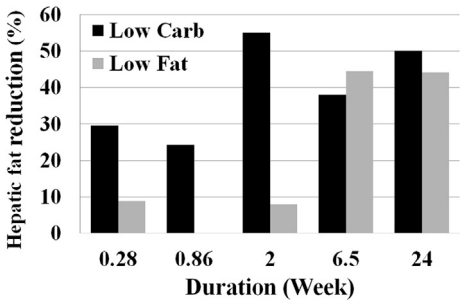

Fig. 6. The relation between the duration of low-carbohydrate diet and hepatic fat reduction. Abbreviations: Low carb, Low-carbohydrate diet group; Low fat, low fat diet group.

4. Discussion

The findings of our meta-analysis suggested that no significant difference between low carbohydrate diet and low fat diet exists in terms of hepatic fat reduction and liver chemistry improvement in NAFLD patient. Although there is one meta-analysis available, it did not compare changes in hepatic fat and liver chemistry to low fat diet and only evaluated the efficacy of low carbohydrate diet in single-arm meta-analysis. To the best of our knowledge, this is the first meta-analysis on low carbohydrate diet in NAFLD that compared low carbohydrate diet to low fat diet. High heterogeneity was observed as we expected. The studies that we found were few in number and had varied clinical outcomes. To explain the various results, we reviewed the design of studies with respect to the ratio of carbohydrate, the method for assessing the liver and duration of the diet. The main reason for discrepancy among the studies measuring the hepatic fat changes by MRS was the duration of diet.

The interesting point is that among the four randomized controlled trials using MRS, two trials [14,18] that were conducted within 2 weeks claimed the effectiveness of low carbohydrate diet. The low-carbohydrate diet group of these two studies reduced intrahepatic fat by 29.6% and 55% after undergoing 48 h and 2 weeks diet program respectively, whereas the low fat diet group reduced intrahepatic fat by 8.9% and 8% respectively. Other two

trials that underwent the diet program for 6 weeks and 6 months showed no significant difference in decrease in intrahepatic lipid between low carbohydrate diet and low fat diet. The carbohydrate intake of these four studies were in the range of 8%–25%, which is relatively very low in terms of carbohydrate consumption.

Ten out of eleven studies that were included in our meta-analysis showed significant weight loss after participation in diet program, and there was no significant difference in weight loss between low carbohydrate diet and low fat diet. Three studies did not restrict calorie intake but the subjects of these studies showed significant weight loss [12,14,21]. Two studies modulated the subjects to lose the same level of weight during the intervention [13,18].

Considering the characteristics of NAFLD, long-term RCTs of at least 1 year study period are needed. Furthermore, a careful review of the adverse effects of long-term changes in macronutrient composition is needed. All studies conducted for ≤6 months have had some problems in evaluating the long-term efficacy and safety of the low-carbohydrate diet. First, there was only one study on liver inflammation and fibrosis assessed with biopsy [21]. Most of the studies used MRS to evaluate intrahepatic fat mass or chemotherapy alone to estimate liver function improvement. These are insufficient for evaluating the accurate function of the liver. Second, the specific type of fat was not analyzed. The type of fatty acid suggests an important role in fatty liver development and intrahepatic inflammation. Even if the same amount of calories was ingested, the amount of fat in the liver and the degree of inflammation may vary depending on the amount and type of fat [22,23]. Intake of n-3 long-chain polyunsaturated fatty acids is used in the treatment of NAFLD in clinical trials [24]. In some studies, the type of fat ingestion was suggested. The study by Browning et al. [14], which showed a successful reduction of intrahepatic fat mass as measured with MRS after an intervention with a low-carbohydrate diet, did not show a difference between saturated fatty acid and unsaturated fatty acid ratios. In the study by Ryan et al. [20], the 40% carbohydrate diet group had a significantly higher rate of unsaturated fatty acid intake than the 60% carbohydrate diet (monounsaturated fat, $P < 0.01$; polyunsaturated fat, $P = 0.01$), and also showed improved ALT. Third, another unresolved issue concerning the low-carbohydrate diet is the increased risk of cardiovascular events associated with long-term ultra-low carbohydrate diets. Unlike previous theories, a meta-analysis study suggested that, in some cases, saturated fat was not associated with an increased risk of cardiovascular disease [25,26]. However, more evidence-based studies have reported that overconsumption of saturated fats and trans-fats increases the risk for cardiovascular disease and associated mortality [7]. In a large cross-sectional study of dietary habits in patients with NAFLD, the intake of saturated and trans fatty acids was consistently higher than that of normal controls, whereas the intake of unsaturated fatty acids, known to reduce intrahepatic fat mass, was low [22,23]. In addition, the potential dangers of fat are known to increase the risk of other chronic diseases as well as the risk of cardiovascular diseases.

In the literature on the low-carbohydrate high-fat diet in patients with NAFLD, the number of subjects was small, the study period was <6 months, and the criteria for carbohydrate intake were variable. Moreover, no RCT used liver biopsy. Therefore, there remains little evidence supporting that the low-carbohydrate diet is superior to the low-fat diet in the management of fatty liver disease. The low-carbohydrate diet seems to increase the protein intake ratios and satiety, and leads to a decrease in total caloric intake. Nevertheless, long-term clinical data of >2 years maintenance of a very low-carbohydrate high-fat diet are insufficient.

In conclusion, to present the evidence of low-carbohydrate diet as a treatment of NAFLD is still lack, additional investigations and evidence-based studies should be conducted to evaluate its long-term stability. Most current studies focused on the efficacy of the very-low-carbohydrate diet; however, long-term feasibility and safety data of the very-low-carbohydrate diet are needed.

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Conflict-of-interest statement

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Author contributions

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