Review Article

The effects of low carbohydrate diets on liver function tests in nonalcoholic fatty liver disease: A systematic review and meta-analysis of clinical trials

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Background: Although several observational and experimental studies have examined the effects of low carbohydrate diets (LCDs) on nonalcoholic fatty liver disease (NAFLD), there are considerable inconsistencies among studies. We summarized the effect of LCDs on liver function tests, including intrahepatic lipid content (IHLC), alanine transaminase (ALT), aspartate aminotransferases (AST), and gamma-glutamyl transferase (GGT) in patients with NAFLD. **Materials and Methods:** PubMed, ISI Web of Science, Scopus, and Google Scholar databases were searched for relevant publications until July 2014, resulting in ten relevant papers that were included in meta-analysis. Related articles were found by searching Medical Subject Heading terms of "NAFLD" in combination with "low carbohydrate." For this meta-analysis, we used mean differences and standard errors of liver function biomarkers. Summary effect and corresponding confidence interval (CI) were estimated using random effect models. Heterogeneity between studies was assessed using Cochran's Q- and I-squared tests. **Results:** Our search led to ten eligible papers that evaluated serum ALT levels (n = 238), nine reported serum AST levels (n = 216), five reported serum GGT concentrations (n = 91), and four assessed IHLC (n = 50). LCD decreased IHLC by −11.53% (95% CI: −18.10, −4.96; I^2 = 83.2%). However, the effect of LCD on liver enzymes was not significant. Mean differences for the effects of LCDs on ALT, AST, and GGT were −4.35 IU/L (95% CI: −12.91, 4.20; I^2 = 87.9%), −1.44 IU/L (95% CI: −4.98, 2.10; I^2 = 61.4%), and −7.85 IU/L (95% CI: −29.65, 13.96; I^2 = 99.4%), respectively. **Conclusion:** LCD consumption in subjects with NAFLD led to a significant reduction in IHLC, but did not significantly affect the concentration of liver enzymes.

Key words: Alanine transaminase, aspartate aminotransferases, glutamyl aminotransferase, liver fat content, low carbohydrate diet, nonalcoholic fatty liver

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is currently the most prevalent liver disorder in developed countries.[1] At the same time, the prevalence rate is increasing both in developed and developing countries.[2-4] The "two-hit hypothesis" suggests that the combined effect of an impaired fatty acid metabolism as well as pro-oxidative and hepatotoxic events is a probable explanation for NAFLD.[5]

Low carbohydrate and low fat diets have been the focus of diet therapies for NAFLD in recent years.[6-8] There is a debate about the optimal diet for the treatment of NAFLD. However, since a low carbohydrate diet (LCD) has greater beneficial effects on daylong

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insulin concentration,[9,10] it appears that LCDs are more effective in improving liver function tests than low fat diets.[11] According to the definition of LCD by the American Diabetes Association, we considered LCDs to be diets in which 26–45% of total daily energy intake is provided by carbohydrates.[12]

In recent years, several studies have examined the effect of LCDs on liver function in NAFLD; however, findings are inconsistent.[13-22] Almost all observational studies have shown a significant positive association between carbohydrate intake and NAFLD.[23-25] Findings from several clinical trials have suggested that LCDs improve biochemical markers of liver function;[6,13,17,22] however, other investigators have not found such effects.[16,19,20] These discrepancies across studies might be related to methodological differences in terms of the weight loss program, macronutrient composition, population, or study duration.

Although there have been several clinical trials, we are aware of no meta-analysis of these trials regarding the effect of LCDs on liver enzymes and fat content in NAFLD. Therefore, in the present study, we conducted a meta-analysis of clinical trial data to summarize the effects of LCDs on liver function tests in NAFLD.

MATERIALS AND METHODS

Search strategy

We searched MEDLINE (http://www.pubmed.com), ISI Web of Science (http://www.webofscience.com), Scopus (http://www.scopus.com), and Google Scholar (http://www.scholar.google.com) databases for relevant clinical trials published until July 2014. In addition, we searched the reference lists of relevant original and review articles to find other suitable studies to be included in this meta-analysis. In the search strategy, we selected keywords from Medical Subject Headings. The search terms included were: "NAFLD" or "nonalcoholic steatohepatitis" or "fatty liver" and "low carbohydrate" or "diet, carbohydrate-restricted" or "ketogenic diet" or "diet, high-fat," or "diet, high-protein." We restricted our search to clinical trials, but did not apply any restrictions regarding the time of publication or language. The present meta-analysis is based on PRISMA guidelines.

Inclusion criteria

We defined LCD as a diet with carbohydrates representing <50% of total energy intake. No restrictions were made on the type or amount of replacement of carbohydrate in the LCDs. Therefore, we included studies if they (1) were conducted in NAFLD adults, (2) reported exact information regarding the dietary content, (3) the prescribed diet contained <50% carbohydrate of total daily energy intake, and (4) reported serum concentration of at least one of the liver enzymes (alanine transaminase [ALT], aspartate aminotransferases [AST], gamma-glutamyl transferase [GGT]), or liver fat content). We included pre-post, parallel, and cross-over trials. A total of ten trials met the eligibility criteria. Data extraction was performed by one of the investigators and reviewed by another. Discrepancies were resolved by discussion with a third reviewer.

Excluded studies

We excluded studies if they (1) were animal or *in vitro* models, (2) examined other types of liver diseases other than NAFLD (such as alcoholic fatty liver, liver injury, liver transplantation, or hepatitis), or (3) were lifestyle interventions without any information about the participants' diets. We also excluded some studies that prescribed 50% or more of total energy from carbohydrates.

Data extraction

Two authors independently reviewed the identified titles and abstracts to select relevant papers from which to extract the following information: First author's last name, publication year, study design, sample size, participants' age, gender, serum levels as methods to assess ALT, AST, GGT and liver fat content, dietary intervention, study duration, and selection criteria such as participants' body mass indexes (BMIs) and chronic disease histories. Information about weight loss or lifestyle changes and physical activity was also abstracted. When dietary carbohydrate intake was reported as gram/day, we converted it to carbohydrate percentage of total energy intake.[13] A pilot study conducted by Tendler *et al*.[15] had individually reported baseline and end values of ALT and AST for a total of five subjects. Using their data, we calculated mean differences in SPSS version 20 (SPSS Inc., Chicago IL, USA). For one study, which was conducted among both NAFLD and healthy-obese patients,[21] only data for NAFLD patients were included in our review. We calculated the standardized mean difference by using the postintervention data for studies that reported only baseline and final outcome values, but did not provide any information regarding mean change.[13,16-22]

Statistical analysis

For this meta-analysis, we used standardized mean differences and standard errors (SEs) of liver function biomarkers including ALT, AST, GGT, and liver fat content. We used random effects model that took into account between-study variation to calculate summary mean estimates and their corresponding SEs, as described by DerSimonian and Laird.[26] Heterogeneity between studies

was assessed using Cochran's Q- and I-squared tests.[27] Heterogeneity was considered important where I^2 was more than 50%. To identify the source of heterogeneity, we performed subgroup analyses. A fixed-effect model was used to assess the subgroup heterogeneity. Sensitivity analyses were performed to examine the extent to which inferences might be related to a particular study or a group of studies. Visual inspection of funnel plots was performed to assess publication bias.[28] Formal statistical assessment of funnel plot asymmetry was done with Egger's regression asymmetry test and Begg's adjusted rank correlation test.[29] Statistical analyses were done using Stata, version 11.2 (Stata Corp., College Station, TX, USA). $P < 0.05$ was considered statistically significant.

Study characteristics

A description of the main characteristics of the included papers is displayed in Table 1. Of 1641 articles retrieved, we identified thirty as being potentially relevant by checking the titles and abstracts. Thirteen studies had not reported exact information regarding dietary interventions and the proportion of macronutrients. Seven studies administrated high carbohydrate diets (>50%). Finally, we included ten randomized clinical trials in the present meta-analysis.[13-22] Figure 1 presents how paper selection was performed in this review. All the ten eligible papers evaluated serum ALT levels ($n = 238$), nine reported serum AST levels ($n = 216$) (all except for Ryan *et al*. 2013[18]), five reported serum GGT concentrations ($n = 91$),[13,16,18,20,21] and four assessed intrahepatic fat content ($n = 50$).[13,16-18] Modified Jadad scale was used to evaluate the study quality.[30] All parallel and cross-over studies achieved eight stars and all pre-post studies achieved four stars.

Some interventions included other components in addition to administering an LCD. In one of these studies, the mean values of dietary cholesterol and SFA intake decreased significantly at the end of the trial.[20] Huang *et al*. encouraged participants to increase dietary fiber intake[19] and Volynets *et al*. aimed to reduce daily fructose intake by 50% compared to participants' usual intake.[13] One study prescribed LCD in the context of a Mediterranean diet that was high in monounsaturated fatty acid (from olive oil) and n3-polyunsaturated fatty acid (n3-PUFA) (from plant and marine sources).[18]

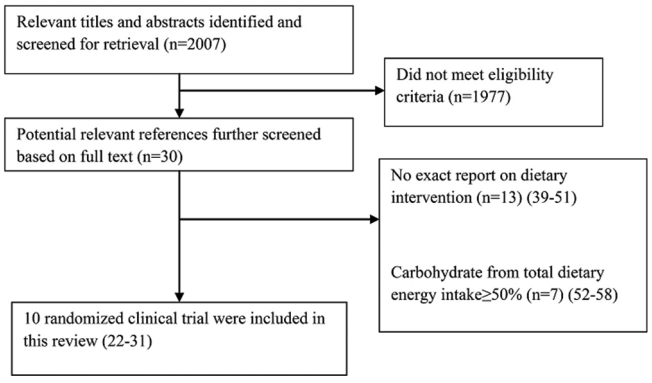


Figure 1: Schematic diagram of article selection

RESULTS

Findings from systematic review

Of the ten studies included in the systematic review and meta-analysis, five studies were conducted in the United States, four studies in European countries, and one study in Asia. All studies were conducted among participants older than 18 years. Five studies (two before-after and three parallel studies) reported a significant decrement in serum ALT levels by administrating LCD,[13,14,20-22] while others did not report any significant changes.[15-19] The results of three parallel and two before-after studies also showed a significant reduction in AST levels,[13,14,16,17,22] but AST reduction by other studies was not significant.[15,19-21] Serum GGT levels decreased significantly only in two studies,[20,21] but did not reach significant level in other studies.[13,16,18] Intrahepatic liver fat content has been significantly ameliorated in three of the four studies which measured liver fat content.[13,17,18] The presence of NAFLD at baseline was ascertained by biopsy in two studies,[15,19] by elevated liver enzymes in three studies,[16,21] and by imaging in four studies.[13,17,18,20,22] Participants in all studies were obese and the mean value of BMI in intervention group ranged from 29.6 kg/m^2 in a study by Kani *et al*.[14] to 38.7 kg/m^2 in a study by Rodríguez-Hernández *et al*.[22]

Findings from meta-analysis

The preliminary results indicate a nonsignificant reduction in serum ALT levels (mean difference [MD] = −4.35 IU/L; 95% confidence interval (CI): −12.91, 4.20). However, significant heterogeneity was revealed among studies ($I^2 = 87.9\%$). To identify the source of heterogeneity, we performed subgroup analyses based on study design (pre-post and parallel or cross-over trials). Heterogeneity remained significant in parallel, but not for pre-post studies ($I^2 = 91.8\%$ for parallel or cross-over trials and $I^2 = 47.9\%$ for pre-post interventions) [Figure 2]. Significant heterogeneity was observed between two subgroups ($I^2 < 0.0001$). After subgroup analyses, we observed a significant reduction in mean serum ALT level (MD = −11.33 IU/L; 95% CI: −18.10, −4.56), though this effect in parallel or cross-over randomized controlled trials was not significant (3.96 IU/L; 95% CI: −9.28, 17.20). Sensitivity analyses revealed that removal of a study by de Luis *et al*.[21] eliminated the heterogeneity among parallel trials ($I^2 = 40.7\%$, $P = 0.167$). Nevertheless, the overall effect did not reach significance (−3.31 IU/L, 95% CI: −9.11, 2.49). Removal of Tendler *et al*. and Browning *et al*. studies, which assessed

Table 1: Characteristics of trials included in the meta-analysis on the effects of carbohydrate restriction on liver function tests in subjects with NAFLD

Author	Subjects and gender	Age (mean±SD)	Study design	Duration (weeks)	Intervention diet	Control diet	Carbohydrate%/ weight loss (kg)		Variables presented	Results
							Intervention	Control		
Ryan *et al*. (2013)	6 Female/ 6 Male	55±14	Randomized, cross-over	6	Mediterranean diet (CHO: 33.6%, Pr: 15.8%, Fat: 44.3%)	CHO: 48.9%, Pr: 23.5%, Fat: 20.7%	33.6±2.4/−1	48.9±2.9/ −2.4	Baseline and end values (SD) of ALT, GGT and IHL, and change of IHL (SD)	LCD reduced significantly liver fat content but not ALT and GGT
Volynets *et al*. (2013)	6 Female/ 4 Male	45.5	Pre-post	25.7	A moderate weight reduction focusing on reducing fructose by 50%	-	38.2 (31.6-57.7)/ −1.9	-	Baseline and end values (SD) of ALT, AST, GGT and IHL (figure-contact), and change of IHL (SD)	LCD reduced significantly liver fat content, ALT and AST but not GGT
Hashemikani *et al*. (2013)	24 Female/ 21 Male	48.8±3.6	Randomized parallel clinical trial	8	Low calorie-Low CHO	CHO: 55.4%, Pr: 315.0%, Fat: 30.0%	43.7±5.1	56.1±5.3	Changes, baseline and end values (SE) of ALT and AST	LCD reduced significantly ALT and AST
Rodriguez-Hernandez *et al*. (2011)	54 Female	46.3±9.1	Randomized but not controlled parallel trial	25.7	Low CHO diet and Exercise at least 1 hr/d for 5 d/week (CHO: 45.0%, Pr: 27.0%, Fat: 28.0%)	CHO: 54.0%, Pr: 25.0%, Fat: 21.0%	45/−5.7	54/-5.5	Baseline and end values (SD) of ALT, AST	LCD reduced significantly ALT and AST
Browning *et al*. (2011)	13 Female/ 5 Male	42±11	Randomized parallel clinical trial	2	Ketogenic diet (CHO: 8.0%, Pr: 33.0%, Fat: 59.0%)	CHO: 50.0%, Pr: 16.0%, Fat: 34.0%	8±5/−5.0	50±4/ −4.0	Baseline and end values (SD) of ALT, AST and change of IHL (SD)	LCD reduced significantly liver fat content and AST but not ALT
de Luis *et al*. (2010)	22 Female/ 7 Male	46.8±15.9	Randomized parallel clinical trial	12.8	Low calorie-Low CHO (CHO: 38.0%, Pr: 26.0%, Fat: 36.0%)	CHO: 53.0%, Pr: 20.0%, Fat: 27.0%	38/−5.0	53/−4.1	Baseline and end values (SD) of ALT, AST and GGT	LCD reduced significantly ALT and GGT but not AST
Elias *et al*. (2010) (adhere)	9 Female/ 8 Male	47.6±12.9	Pre-post	25.7	Weight loss diet (CHO: 46.9%, Pr: 20.4%, Fat: 32.6%)	-	46.9±7.5/ −8.2	-	Baseline and end values (SD) of ALT, AST and GGT	LCD reduced significantly ALT and GGT but not AST
Elias *et al*. (2010) (non-adhere)	7 Female/ 7 M	47.4±10.0	Pre-post	25.7	Weight loss diet (CHO: 47.9%, Pr: 20.8%, Fat: 30.5%)	-	47.9%±6.0/ −1.6	-	Baseline and end values (SD) of ALT, AST and GGT	LCD did not significantly change ALT, AST and GGT
Tendler, *et al*. (2007)	3 Female/ 2 Male	24-50 years	Pilot and Pre-post study	24	Ketogenic diet (CHO <20 g/d)	-	<20 g/d/ −12.82	-	Baseline and end values (SD) of ALT and AST	LCD did not significantly reduce ALT and AST
Thomas *et al*. (2006)	*n*=10	-	Pre-post	25.7	Weight loss diet (CHO: 46%, Pr: 18%, Fat: 35%)	-	46±4/−3.3	-	Baseline and end values (95%CI) of ALT, AST and GGT	LCD reduced significantly AST but not liver fat content, ALT and GGT
Huang *et al*. (2005)	8 F/8 M	49.8±12	Pilot study, Pre-post	25.7	CHO: 40-45%, Pr: 15-20%, Fat: 35-40%	-	40-45/−3.3	-	Baseline and end values (SE) of ALT and AST	LCD did not significantly reduce ALT and AST

ketogenic diet,[15,17] did not eliminate heterogeneity among parallel or cross-over trials [Supplementary Figure 1].

Our analysis of nine eligible studies[13-17,19-22] that assessed serum AST level indicated that among 216 subjects, the overall pooled estimated MD was −1.44 IU/L (95% CI: −4.98, 2.1). However, there was substantial between study heterogeneity (I^2 = 61.4%). Subgroup analyses based on this study design eliminated heterogeneity among pre-post studies (I^2 = 0.0%), but it remained significant among parallel studies (I^2 = 85.2%) [Figure 3]. Significant heterogeneity was observed between two subgroups (I^2 < 0.0001). Heterogeneity disappeared with removal of the study by de Luis *et al*.[21] (I^2 = 0.0%). The results of subgroup analyses demonstrated a significant reduction in serum AST level in pre-post studies (−2.48 IU/L; 95% CI: −4.40, −0.56), but the effect was not significant for parallel studies (1.85 IU/L; 95% CI: −6.99, 10.70); furthermore, removal of study by de Luis *et al*.[21] led to a significant reduction in the overall effect in parallel studies (−4.91 IU/L; 95% CI: −7.87, −1.94). Removal of studies by Tendler *et al*. and Browning *et al*.,[15,17] which assessed ketogenic diets, did not eliminate heterogeneity among parallel or cross-over studies [Supplementary Figure 2].

The overall effect for GGT was 7.85 IU/L (95% CI: −29.65, 13.96) and the heterogeneity was significant (Cochrane Q-test, P < 0.001, I^2 = 99.4%) [Figure 4]. We could not eliminate the heterogeneity based on study design by subgroup analysis in spite of significant heterogeneity between two subgroups (I^2 < 0.0001). The overall effect in parallel or cross-over trials was − 11.76 IU/L (95% CI: −51.45, 27.93, I^2 = 99.9%). The results of pre-post studies showed a nonsignificant reduction in serum GGT levels (−6.84 IU/L; 95% CI: −20.73, 7.04, I^2 = 82.3%). Sensitivity analysis excluding each specific study did not substantially alter these results.

We found that LCDs significantly decreased liver fat content in a total of fifty adults in four studies[13,16-18] (MD = −11.53%; 95% CI: −18.10, −4.96). However, the results of the Q-test showed a considerable heterogeneity among studies (Cochrane Q-test, P < 0.001, I^2 = 83.2%). When the subgroup analysis was performed based on the study design, we observed no significant heterogeneity in any of the groups (pre-post studies: I^2 = 0.0% and parallel or cross-over studies: I^2 = 13.1%), while the heterogeneity was significant between the two subgroups. The results of subgroup analyses showed that both pre-post as well as parallel or cross-over study designs effectively reduced liver fat content with a slightly greater reduction in parallel or cross-over trials (MD = −11.53 IU/L; 95% CI: −18.10, −4.96 for pre-post studies and MD = −18.33; 95% CI: −24.99, −11.67 for parallel or cross-over studies) [Figure 5]. Sensitivity analysis excluding each specific study did not substantially alter these results.

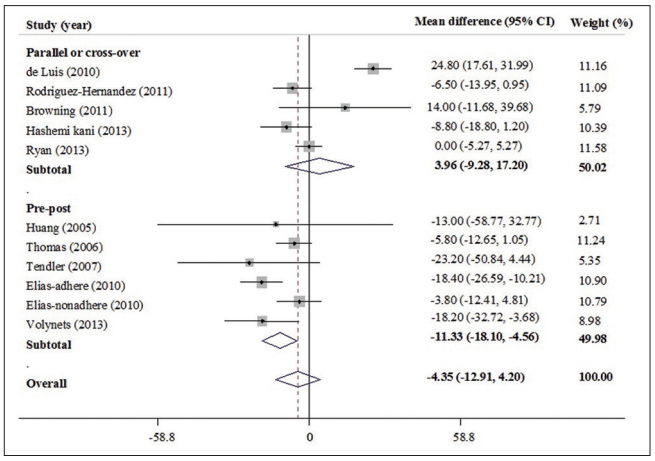


Figure 2: Forest plot showing the overall effect of low carbohydrate diet on serum alanine transaminase levels in subjects with nonalcoholic fatty liver disease and subgroup analysis based on study design (parallel or cross over and pre-post studies using random effects model)

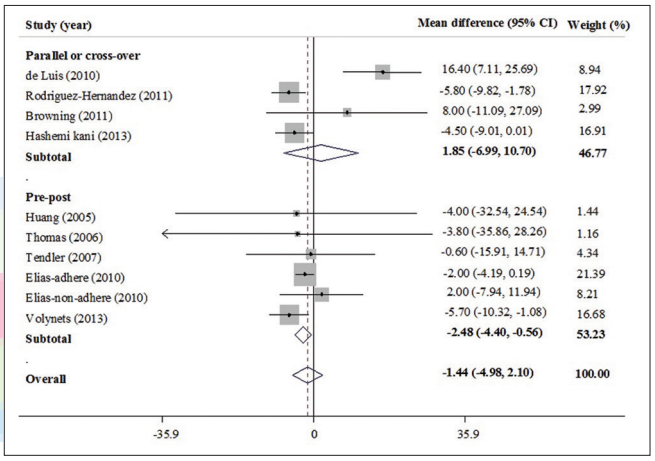


Figure 3: Forest plot showing overall effect of low carbohydrate diet on serum aspartate aminotransferases levels in subjects with nonalcoholic fatty liver disease and subgroup analysis based on study design (parallel or cross over and pre-post studies using random effects model)

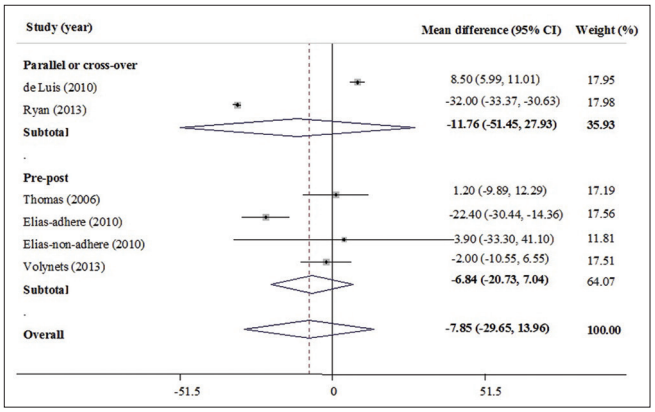


Figure 4: Forest plot showing overall effect of low carbohydrate diet on serum gamma-glutamyl transferase levels in subjects with nonalcoholic fatty liver disease and subgroup analysis based on study design (parallel or cross over and pre-post studies using random effects model)

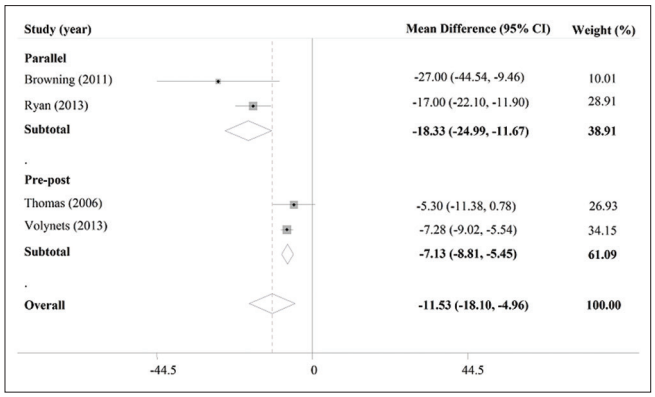
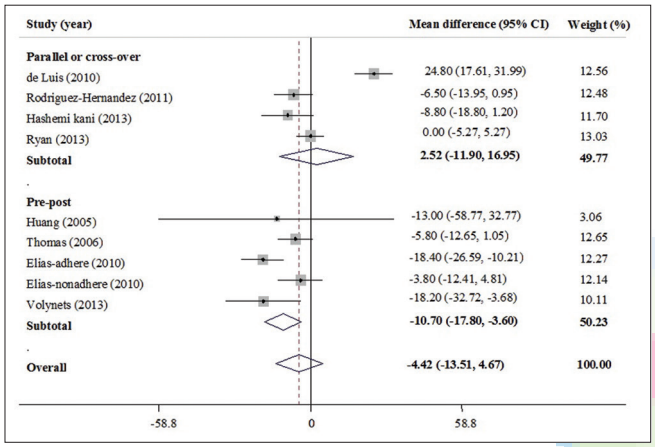
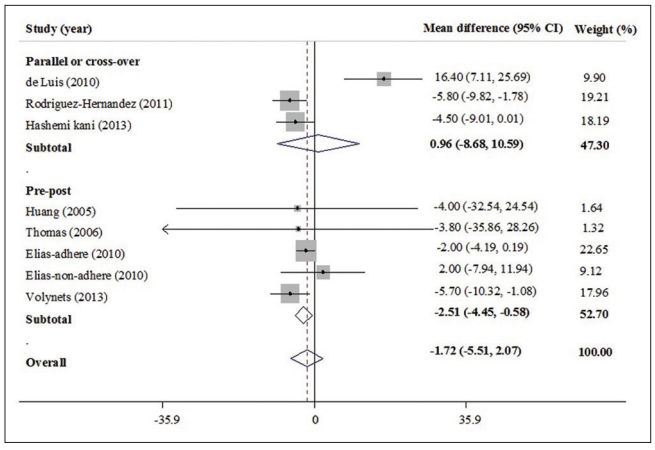


Figure 5: Forest plot showing overall effect of low carbohydrate diet on liver fat content levels in subjects with nonalcoholic fatty liver disease and subgroup analysis based on study design (parallel or cross over and before-after studies using random effects model)



Supplementary Figure 1: Forest plot showing overall effect of low carbohydrate diet on serum alanine transaminase levels after removing ketogenic diets in subjects with nonalcoholic fatty liver disease and subgroup analysis based on study design (parallel or cross over and pre-post studies using random effects model)



Supplementary Figure 2: Forest plot showing overall effect of low carbohydrate diet on serum aspartate aminotransferases levels after removing ketogenic diets in subjects with nonalcoholic fatty liver disease and subgroup analysis based on study design (parallel or cross over and pre-post studies using random effects model)

Publication bias

Although there was a slight asymmetry in Begg's funnel plot, we did not find any evidence of publication bias for ALT (Egger's test, $P = 0.52$, Begg's test, $P = 0.44$), AST (Egger's test, $P = 0.38$, Begg's test, $P = 0.59$), GGT (Egger's test, $P = 0.86$, Begg's test, $P = 0.99$), or liver fat content (Egger's test, $P = 0.34$, Begg's test, $P = 0.5$).

DISCUSSION

Findings from the present meta-analysis indicate that consumption of LCDs (with <50% of calories from carbohydrate) in NAFLD patients did not reduce the serum concentration of liver enzymes, but reduced the liver fat content. However, based on subgroup analyses, we found that studies with pre-post designs reported a favorable effect of LCDs on ALT, AST, and liver fat content, but not on serum GGT level. The results of parallel and cross-over studies showed nonsignificant effects on liver transaminase, but like pre-post studies, they also reported a beneficial effect on reducing liver fat content. There was a significant heterogeneity for the change in ALT and AST, due to the large significant increase in these enzymes in de Luis *et al*.'s 2010 study. Although ALT showed a reduction after the removal of de Luis *et al*.'s study, the mean change was not significant.

Although Rodríguez-Hernández *et al*.[22] showed that weight reduction improved the serum level of aminotransferase irrespective of dietary macronutrient composition (LCD or low fat diet), other investigators found that beside weight reduction, LCD had a greater number of beneficial effects on treatment of patients with NAFLD compared to a high carbohydrate diet.[15,17,19-21] However, others have shown that dietary macronutrient composition was an independent determinant of intrahepatic fat content.[17,18] A possible explanation for beneficial effects of carbohydrate-restricted diets in subjects with NAFLD may be related to enhanced lipid oxidation that is induced by energy and carbohydrate restriction.[17,31] In addition, dietary carbohydrate has a primary role in lipogenesis; therefore, the strong association between hepatic fat content and dietary carbohydrate may be a consequence of decreased hepatic *de novo* lipogenesis from LCDs. Although our meta-analysis showed that LCDs significantly reduced liver fat content, liver enzyme changes did not reach statistical significance. It should be noted that ALT is not sufficiently sensitive to detect low levels of liver fat.[32] Studies included in the present meta-analysis enrolled subjects with different liver fat content levels. Furthermore, the direct link between ALT and intra-abdominal adipose tissue may affect the ALT response to dietary interventions.[16]

Another determinant of change in liver enzymes might be related to hepatic fat content, since some investigators have reported lower ALT and AST levels in patients with improved liver histology.[19] Other possible reasons for the variation in transaminase response may be related to the half-life of enzymes, elevated sinusoidal clearance, cytosolic

or mitochondrial secretion, and differences in hepatic metabolic activity.[33,34] However, it seems that improved insulin resistance as a consequence of LCDs[13,18,20] may be one of the main reasons for improvement in liver parameters.[35-37]

The heterogeneity between studies could be attributable to different causes. Possible reasons for heterogeneity include the amount of weight loss and especially waist circumference decrement, the method of weight reduction (e.g., exercise, calorie restriction to a fixed amount (1200–1500 kcal/d for all subjects) or 500–1000 kcal/d less than the required amount, the amount of carbohydrate restriction, diversity in liver function tests, differences in study populations because of dietary history and pattern of fat distribution, type of replacements used for restricted carbohydrates, type of macronutrients, or other differences in study design. We were not able to perform subgroup analyses to examine these sources of heterogeneity except in terms of study design. To evaluate other sources of heterogeneity, more research is needed. In the present meta-analysis, there were only two studies that did not attempt to reduce body weight.[15,18] However, in one study lasting for 24 weeks, a significant weight reduction was observed for most participants[15] and in another that lasted for 6 weeks, weight loss occurred, but the reduction was not statistically significant.[18] Therefore, because weight reduction occurred in almost all studies, we could not isolate the effect of weight loss on NAFLD from the effects of LCD.

Two studies in our meta-analysis evaluated the effects of the Atkin's diet,[15,17] which is a very LCD. One study prescribed 8% of total daily energy intake[17] and another study recommended 20 g of carbohydrate per day.[15] In other published studies, the average range of carbohydrates in the LCD was between 33.6% and 46.9% as compared with 48.9–54.0% in the control diet. Only one study had a control group that consumed <50% carbohydrate.[18] However, we included it in our analysis because there was a large and significant difference between the carbohydrates prescribed in intervention and control groups (33.6% vs. 48.9%).

Several points must be considered when interpreting our findings. First, in most studies included in our meta-analysis, weight reduction was an intended outcome. However, dietary carbohydrate restriction may ameliorate the beneficial effect of hypocaloric diets on liver function tests in subjects with NAFLD. Second, there was a considerable difference across studies regarding dietary composition. It is possible that the replacement of carbohydrate in different studies affects the outcomes of LCDs. Therefore, it is impossible to isolate the effects of specific macronutrients on the endpoints. Third, due to varying health effects of different types of macronutrients (e.g., low- vs. high-glycemic index carbohydrate and n3-PUFA and mono unsaturated fatty acids vs. saturated fatty acids), dietary macronutrient type is another important factor. Fourth, the study duration ranged from 2 weeks[17] to 12 months.[19] However, most studies followed the participants for more than 3 months. Fifth, almost all studies were conducted in Western countries. This is important to note because of distinct obesity patterns in Middle-Eastern countries which are mainly characterized by abdominal obesity and higher visceral adipose tissue[38] as well as differences in dietary patterns and lifestyle. Sixth, one of the major limitations of the studies included in the present meta-analysis was their small sample size that could affect type-2 statistical error, specifically regarding the transaminases.

CONCLUSION

Our meta-analysis of clinical trials revealed that LCDs improved liver fat content, but not serum liver enzyme levels in subjects with NAFLD. However, there are many sources of heterogeneity that should be considered, for which we were not able to perform subgroup analyses.

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Conflicts of interest

There are no conflicts of interest.

AUTHORS' CONTRIBUTION

FH and LA contributed in conception. FH and AS contributed in search, data extraction, and analysis. FH and LA contributed in drafting the manuscript. PJS contributed in language editing of manuscript. All authors approved the final manuscript for submission.

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