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Ketogenic, hypocaloric diet improves nonalcoholic steatohepatitis

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ABSTRACT

Background and objectives: Nonalcoholic steatohepatitis (NASH) is strongly associated with obesity. A weight loss of ≥10% is necessary to improve NASH severity, but this goal has rarely been achieved in published studies using different diet protocols. The effect of a ketogenic, hypocaloric, commercial diet ("Ideal Protein," IP) on body weight, metabolic markers, and liver tests in a group of NASH patients is evaluated in this study. Daily calorie intake was tailored to achieve a weight loss of ≥10%. **Methods**: We analyzed 38 patients with NASH who were placed on the IP diet between 2014 and 2018 and compared their outcomes with 6 control patients who declined the diet. All patients were evaluated by a trained health coach in weekly intervals throughout the study period. Clinical and laboratory data obtained before and at 6.5 months after intervention were compared using paired t-testing. **Results**: The patients on the IP diet experienced a significant weight reduction (217 ± 8 lb *vs.* 194 ± 7 lb; mean ± S.E.M.), corresponding to an average weight loss of 9.7% ± 1.6%. Significant changes in systolic blood pressure (133 ± 3 mmHg *vs.* 123 ± 3 mmHg), triglycerides (200 ± 21 mmol/L *vs.* 132 ± 11 mmol/L), hemoglobin A1c (6.71% ± 0.29% *vs.* 5.74% ± 0.19%), SGPT (97.3 ± 11.1 IU/L *vs.* 44.2 ± 5.9 IU/L), SGOT (82.4 ± 10.5 IU/L *vs.* 32.8 ± 5.2 IU/L), and Fib-4 scores (2.25 ± 0.23 *vs.* 1.40 ± 0.13) were also observed ($P<0.05$ in all cases). In the IP group, 50.5% of patients lost ≥10% body weight. In contrast, no significant changes were observed in the control group. The IP diet was well tolerated, and no safety signals were noticed. **Conclusions**: A ketogenic, hypocaloric resulted in striking weight loss and significant improvements in metabolic parameters and liver tests, suggesting that this approach carries promise for the dietary management of patients with NASH.

Key words: nonalcoholic fatty liver disease, high-protein diet, metabolic syndrome, Ideal Protein diet, caloric restriction, weight management, lifestyle intervention

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INTRODUCTION

Nonalcoholic steatohepatitis (NASH)—an obligatory precondition for cirrhosis development in patients with fatty liver disease—is strongly associated with obesity, diabetes, and other features of metabolic syndrome.[1] The underlying insulin resistance is considered a key driver of hepatic inflammation and fibrogenesis.[2] Despite the vigorous interest in pharmaceutical treatment options for NASH, there is a general consensus that dietary and lifestyle modifications represent an integral part of the overall treatment plan for the management of the disease.[3] Recent epidemiologic studies and clinical trials have provided evidence that a robust weight loss—at least 7-10%—is necessary to reduce hepatic inflammation and reverse fibrogenesis.[4] This critical weight loss requirement can be achieved with a variety of dietary regimens, including the Mediterranean diet, low-fat diet, or low-carbohydrate diets.[5] However, only a minority of patients with NASH reached the critical weight loss threshold in these studies.

Our institution recently established a comprehensive weight management program that incorporates a commercially

available, hypocaloric ketogenic diet ("Ideal Protein," IP). This program was primarily designed for the management and prevention of cardiovascular disease in obese patients. On the basis of the shared metabolic risk factors of patients with fatty liver disease, we tested the impact of this program in our NASH population. The results of our study suggest that this approach holds promise for patients with NASH.

METHODS

Study population

We searched the electronic medical records for all patients with a prior diagnosis of NASH who had been evaluated in our Hepatology Clinic between January 2014 and July 2018 and who had been referred to our Weight Management Clinic during this time period. The diagnosis of NASH was ascertained by a variety of tests, including liver biopsy, transient elastography ("FibroScan"), magnetic resonance elastography, and characteristic liver test abnormalities, following standard clinical guidelines.[6] Patients with stable, NASH-related cirrhosis were included. Patients with concomitant chronic liver disease caused by HBV or HCV infection, autoimmune liver diseases, hemochromatosis, Wilson disease, lipodystrophy, abetalipoproteinemia or patients taking medications known to induce hepatic steatosis were excluded. Patients with a documented history of hyperuricemia, nephrolithiasis, ketoacidosis, or cardiac arrhythmias were excluded. In addition, patients with an average daily alcohol intake of more than one standard drink were excluded. This study was approved by the Institutional Review Board of NorthShore University HealthSystem. We identified 43 patients who met the inclusion criteria.

Weight management program

We used a comprehensive weight management strategy that is based on a calorie-restricted, ketogenic, moderate-fat/moderate-protein diet, in conjunction with intense counseling and close follow-up. The diet is commercially available in the United States and other countries (IP). The weight management program consists of four phases, with the first phase designed to achieve the weight loss goal and the subsequent phases aimed at maintaining and stabilizing the initial weight loss.

The IP diet preferentially incorporates carbohydrates with a low glycemic index (primarily vegetables) and lean meats and fish as preferred protein and fat sources, respectively. Olive and grape seed oils represent the major sources of fatty acids. The macronutrient profile of the IP diet is 50% fat, 30% protein, and 20% carbohydrates. In addition, patients receive daily omega-3 fatty acids, multivitamin, calcium, magnesium, and potassium supplements.

An individual weight loss target corresponding to 10% of the pre-intervention body weight was established for each patient, and the corresponding caloric intake was determined accordingly. On an average, patients consumed 900–1100 kcal/day until their weight loss target was reached. They were given instructions on essential dietary rules, including complete alcohol avoidance. They were also advised on how to prepare one daily meal at home. They were visited by the health coach on a weekly basis, under the supervision of a physician with expertise in weight management. Their weights were recorded, and adjustments to their diets were made at the coach's discretion. We did not routinely measure blood or urinary ketones, although individual patients were encouraged to check urinary ketones at their own discretion.

Monitoring in hepatology clinic

Patients visited the hepatology clinic in 3-month intervals. Their vital signs—including weight and BMI—were recorded at each visit. Blood tests were obtained for metabolic and liver-related tests, including total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, hemoglobin A1c, SGPT, SGOT, albumin, and platelets. Noninvasive fibrosis evaluation was performed using the Fib-4 index.[7]

Study groups and statistical analysis.

Patients were stratified according to their decisions to enroll ("IP group"; $n = 38$) or to decline participation ("control group"; $n = 6$) in the weight management program. Pre- and post-treatment data were analyzed using paired Student t-testing, using a significance level of $P<0.05$.

RESULTS

The two patient groups did not differ significantly with respect to age, sex, or race (Table 1). IP patients experienced a marked weight loss, averaging >9%. Approximately one-half of the IP patients lost ≥10% of their starting weights (Figure 1). The weight loss in the IP group was statistically highly significant. In contrast, no significant weight change was observed in the control patients. The statistical power for the nonsignificant difference in the control patients was 52%, whereas the power for the significant difference in the IP patients was 99%. The difference in power was due to the small sample size of the control group.

Weight loss in the IP group was accompanied by a reduction in systolic blood pressure, with a similar trend in diastolic blood pressures that did not reach statistical significance. In comparison, no blood pressure changes were observed in the control group (Table 1). IP patients experienced significant reductions in glycated hemoglobin and triglyceride levels, with no changes in HDL or LDL

Table 1: Demographic features, weight responses, and changes in laboratory data in NASH control patients and in patients enrolled in the Ideal Protein (IP) weight management program.

	Control Patients (n = 5)			IP Patients (n = 38)		
	Before	**After**	***P*-value**	**Before**	**After**	***P*-value**
Age, years	50.6 ± 5.9			53.6 ± 2.0		n.s.
Sex (female/male), %	40/60			52.6/47.4		n.s.
Race (white/nonwhite), %	80/20			60.53/39.47		n.s.
Body weight, lb	211 + 16	215 + 17	n.s.	217 ± 8	194 + 7	2.20E-11
Body mass index	33 + 2	35 + 2	n.s.	34 ± 1	31 ± 1	9.60E-12
weight loss, %		+2 ± 1			−10 ± 2	<0.0001
weight loss ≥ 10%, %		0			51	
Systolic blood pressure, mmHg	124 + 1	125 + 1	n.s.	133 ± 3	123 ± 3	<0.005
Diastolic blood pressure, mmHg	78 + 1	81 + 1	n.s.	79 ± 1	76 ± 1	0.057
Glycated hemoglobin, %	n.a.	n.a.		7 ± 0.3	6± 0.2	<0.005
Triglycerides, mmol/L	n.a.	n.a.		200 ± 21	132 ± 11	<0.00005
HDL cholesterol, mg/dL	n.a.	n.a.		40 + 5	25 + 5	n.s.
LDL cholesterol, mg/dL	n.a.	n.a.		110 + 9	115 + 9	n.s.
Platelet count, ×1,000/ml	258 ± 18	250 ± 21	n.s.	220 ± 10	204 ± 8	<0.05

NOTE: Quantitative data expressed as mean ± S.E.M. Within-group comparisons were performed using Student's t test. A *P*-value of <0.05 was considered significant.

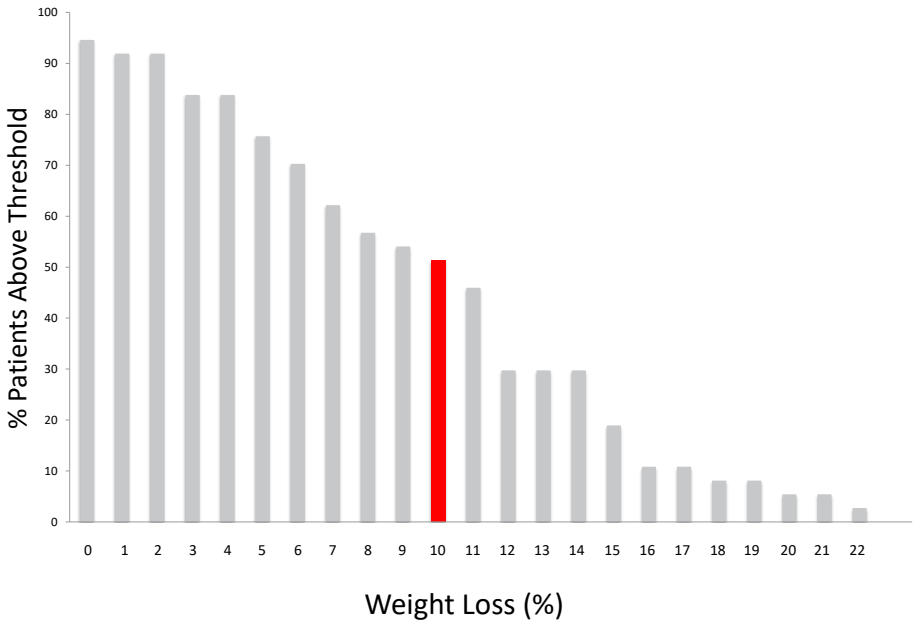

Figure 1: Weight loss distribution in patients on the IP protocol. The figure shows the percentage of IP patients who achieved a weight reduction over a range of thresholds (from 0% to 22%). Approximately 50% of patients achieved a weight loss of ≥10% (red bar).

cholesterol. No changes were observed in the control group. A numerically small (7.3%) reduction in platelet count was observed in the IP group, with no respective change in the control group.

In the IP group, we observed significant reductions in SGPT and SGOT levels, as well as Fib-4 scores, without accompanying changes in serum albumin (Figure 2). No changes in liver enzymes or Fib-4 scores were observed in the control group (data not shown).

DISCUSSION

NASH has emerged as a major public health issue in Western countries. It is projected to become the leading cause of chronic liver disease and its complications, including cirrhosis and hepatocellular cancer, within the next decades.[6] The underlying risk factors for NASH include sedentary behavior, low physical activity, poor diet, and genetic predisposition. Similar to other disease processes related to obesity and metabolic syndrome, improvement of patients' diet is considered a cornerstone of disease management for patients with NASH.[5]

Our study highlights the marked impact of a low-calorie, ketogenic diet on patient's weights, metabolic markers of insulin resistance, liver inflammation, and fibrosis.

In our retrospective analysis, approximately half of the patients achieved or exceeded a weight loss of 10%, considered the critical threshold for the resolution of hepatic inflammation and regression of fibrosis.[8] Weight loss was associated with significant changes in systolic blood pressure, hemoglobin A1c, and triglycerides. Strikingly, we also observed significant decreases in transaminase levels and Fib-4 scores, suggesting a beneficial effect on hepatic inflammation and fibrogenesis.

The high success rate of our program compares favorably with published data from several dietary intervention trials. For example, in the landmark study by Vilar-Gomez and colleagues,[9] 293 Cuban patients with biopsy-confirmed NASH were instructed to consume a low-fat, hypocaloric diet, providing 750 kcal/day less than their estimated daily energy requirements. Patients were regularly counseled with regard to maintaining a healthy lifestyle that included regular, moderate exercise. Although the majority of

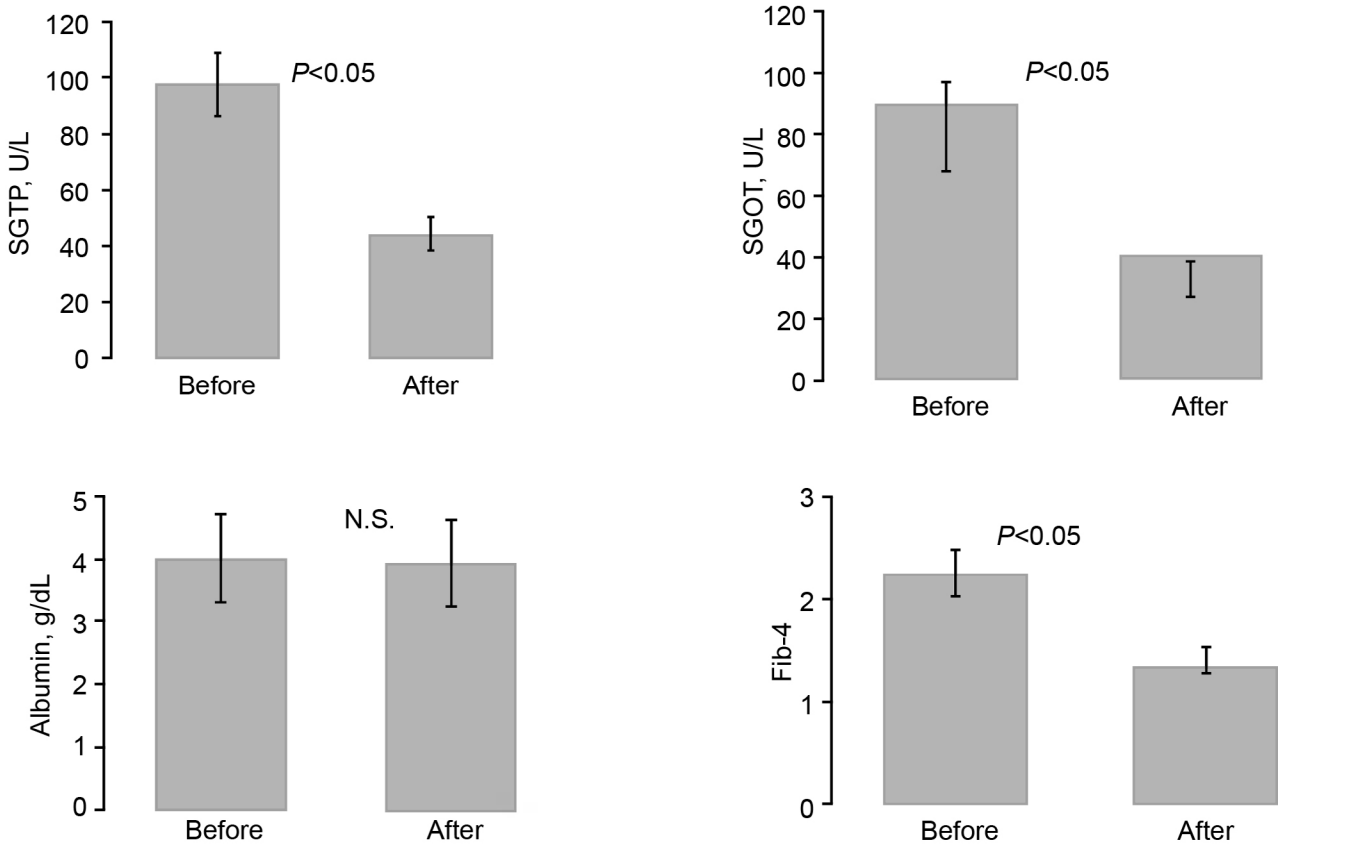

Figure 2: Effect of the IP protocol on liver tests. The figure shows SGPT, SGOT, albumin, and Fib-4 scores before and at the end of the weight loss phase. Data are shown as mean ± S.E.M.

patients experienced a statistically significant weight loss and improvement in liver histology, only 9.8% of patients achieved a weight loss of ≥10%.[9] Our results are also comparable with those reported by Promrat *et al.* who performed a randomized controlled trial on weight loss in patients with NASH.[10] In this study, the treatment group was instructed to consume a hypocaloric diet containing 25% fat, consistent with recommendations by the American Heart Association and the American Diabetes Association. In addition, patients underwent behavioral counseling, and they were encouraged to engage in regular exercise activities. Over the 2-year study period, 40% of patients in the treatment group achieved a weight loss of ≥10%, and this was associated with significant improvements in histologic NASH activity.[10]

We acknowledge that a weight-focused dietary approach may be overly simplistic for outpatient population. Significant improvements in metabolic syndrome and NASH may be achievable by focusing on the composition of the diet, rather than its caloric content. Perhaps the best-studied example in this regard is the "Mediterranean diet," which emphasizes natural unprocessed foods, reduced intake of sweets, red and processed meats, and high intake of olive oil.[11-15] On the basis of its excellent safety profile and beneficial effects on features of metabolic syndrome, the Mediterranean diet has received a first-line endorsement by the European Association for the Study of Liver Diseases (EASL).[16] However, we note that large-scale, prospective trials documenting the efficacy of the Mediterranean diet in patients with NASH are lacking.

Similarly, we consider that the low-carbohydrate/moderate fat composition of the IP diet may exert calorie-independent, beneficial effects. The complex interplay between overall calorie intake and the specific macro- and micronutrient balance has been extensively investigated in the past. [4, 17-22] Several authors have demonstrated that a "simple ketogenic diet" may result in a significant improvement in hepatic steatosis.[23, 24] Similarly, relatively high protein content may exert beneficial effects in fatty liver disease.[25, 26] However, we are skeptical of whether a meaningful improvement in hepatic inflammation and fibrosis can be achieved without calorie depletion in the majority of patients with NASH.

Of note, the IP diet was well tolerated, apart from occasional complaints of constipation or lack of palatability. Unlike most studies of lifestyle intervention in NASH, patients were discouraged from concomitantly increasing their exercise activities in order to avoid excessive protein catabolism that is a hallmark of advanced chronic liver disease. Although the manufacturers of the IP have recommended closer monitoring of patients with liver disease, we did not notice any untoward effects or safety signals in our patient population that included several patients with stable cirrhosis. Along these lines, we specifically excluded patients with decompensated cirrhosis who would be particularly susceptible to protein and calorie malnutrition.

Potential advantages of our approach include the relative simplicity of the treatment protocol. Patients were not required to perform calorie counting or to spend extended amounts of time to procure the "correct ingredients." Frequent interactions with the study coaches were another key feature of our protocol. According to informal feedback from our patients, the counseling sessions were extremely important, especially given the significant physical and mental strain of strict dieting. The importance of frequent, in-person counseling is well documented in the literature and may in fact rival the importance of the specific diet composition.[27]

Our study has several limitations, including its retrospective design and the lack of randomization. The lack of randomization precluded any direct statistical comparison between the IP patients and the control group. In a future randomized clinical trial, we plan on recruiting equally sized case and control populations. It is likely that we selected for highly motivated patients who were likely to adhere to the diet, a feature that would enhance the apparent treatment effect. Another limitation is the lack of a longer-term follow-up period. On the basis of the published literature, a significant percentage of patients regain weight after the successful completion of a hypocaloric loss program. It remains to be seen whether our patients will maintain their weight loss during the "weight stabilization phase" of the IP diet. Another limitation is the lack of pre- and post-treatment fibrosis staging in our patients, which allows for the possibility that significant weight loss might occurred without significant changes in liver disease.

In summary, our data suggest that a hypocaloric, ketogenic diet can bring about significant weight loss and improvements in metabolic syndrome and liver injury and fibrosis in patients with NASH. On the basis of the encouraging results of our pilot study, we are currently planning a randomized prospective study to rigorously evaluate this treatment approach.

Conflict of Interest

The author declares no conflict of interest.

REFERENCES

1. Neuschwander-Tetri BA. Non-alcoholic fatty liver disease. BMC Med 2017;15:45.
2. Petersen MC, Vatner DF, Shulman GI. Regulation of hepatic glucose metabolism in health and disease. Nat Rev Endocrinol 2017;13:572-87.
3. Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. Nat Med 2018;24:908-22.
4. Musso G, Cassader M, Rosina F, Gambino R. Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomised trials. Diabetologia 2012;55:885-904.
5. Romero-Gomez M, Zelber-Sagi S, Trenell M. Treatment of NAFLD with diet, physical activity and exercise. J Hepatol 2017;67:829-46.
6. Spengler EK, Loomba R. Recommendations for Diagnosis, Referral for Liver Biopsy, and Treatment of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis. Mayo Clin Proc 2015;90:1233-46.
7. Shah AG, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ, *et al*. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2009;7:1104-12.
8. Glass LM, Dickson RC, Anderson JC, Suriawinata AA, Putra J, Berk BS, *et al*. Total body weight loss of >/= 10 % is associated with improved hepatic fibrosis in patients with nonalcoholic steatohepatitis. Dig Dis Sci 2015;60:1024-30.
9. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, *et al*. Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis. Gastroenterology 2015;149:367-78.e5; quiz e14-5.
10. Promrat K, Kleiner DE, Niemeier HM, Jackvony E, Kearns M, Wands JR, *et al*. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. Hepatology 2010;51:121-9.
11. Gelli C, Tarocchi M, Abenavoli L, Di Renzo L, Galli A, De Lorenzo A. Effect of a counseling-supported treatment with the Mediterranean diet and physical activity on the severity of the non-alcoholic fatty liver disease. World J Gastroenterol 2017;23:3150-62.
12. Katsagoni CN, Papatheodoridis GV, Ioannidou P, Deutsch M, Alexopoulou A, Papadopoulos N, *et al*. Improvements in clinical characteristics of patients with non-alcoholic fatty liver disease, after an intervention based on the Mediterranean lifestyle: a randomised controlled clinical trial. Br J Nutr 2018;120:164-75.
13. Kontogianni MD, Tileli N, Margariti A, Georgoulis M, Deutsch M, Tiniakos D, *et al*. Adherence to the Mediterranean diet is associated with the severity of non-alcoholic fatty liver disease. Clin Nutr 2014;33:678-83.
14. Misciagna G, Del Pilar Diaz M, Caramia DV, Bonfiglio C, Franco I, Noviello MR, *et al*. Effect of a Low Glycemic Index Mediterranean Diet on Non-Alcoholic Fatty Liver Disease. A Randomized Controlled Clinici Trial. J Nutr Health Aging 2017;21:404-12.
15. Papamiltiadous ES, Roberts SK, Nicoll AJ, Ryan MC, Itsiopoulos C, Salim A, *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.
16. 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;64:1388-402.
17. Jang EC, Jun DW, Lee SM, Cho YK, Ahn SB. Comparison of efficacy of low-carbohydrate and low-fat diet education programs in non-alcoholic fatty liver disease: A randomized controlled study. Hepatol Res 2018;48:E22-9.
18. McGuire S. U.S. Department of Agriculture and U.S. Department of Health and Human Services, Dietary Guidelines for Americans, 2010. 7th Edition, Washington, DC: U.S. Government Printing Office, January 2011. Adv Nutr 2011;2:293-4.
19. Castaldo G, Monaco L, Castaldo L, Galdo G, Cereda E. An observational study of sequential protein-sparing, very low-calorie ketogenic diet (Oloproteic diet) and hypocaloric Mediterranean-like diet for the treatment of obesity. Int J Food Sci Nutr 2016; 67: 696-706.
20. Lu W, Li S, Li J, Wang J, Zhang R, Zhou Y, *et al*. Effects of Omega-3 Fatty Acid in Nonalcoholic Fatty Liver Disease: A Meta-Analysis. Gastroenterol Res Pract 2016;2016:1459790.
21. Parker HM, Johnson NA, Burdon CA, Cohn JS, O'Connor HT, George J. Omega-3 supplementation and non-alcoholic fatty liver disease: A systematic review and meta-analysis. J Hepatol 2012;56:944-51.
22. Toshimitsu K, Matsuura B, Ohkubo I, Niiya T, Furukawa S, Hiasa Y, *et al*. Dietary habits and nutrient intake in non-alcoholic steatohepatitis. Nutrition 2007;23:46-52.
23. Pérez-Guisado J, Muñoz-Serrano A. The Effect of the Spanish Ketogenic Mediterranean Diet on Nonalcoholic Fatty Liver Disease: A Pilot Study. J Med Food 2011;14:677-80.
24. Tendler D, Lin S, Yancy WS, Jr., Mavropoulos J, Sylvestre P, Rockey DC, *et al*. The effect of a low-carbohydrate, ketogenic diet on nonalcoholic fatty liver disease: a pilot study. Dig Dis Sci 2007;52:589-93.
25. Bezerra Duarte SM, Faintuch J, Stefano JT, Sobral de Oliveira MB, de Campos Mazo DF, Rabelo F, *et al*. Hypocaloric high-protein diet improves clinical and biochemical markers in patients with nonalcoholic fatty liver disease (NAFLD). Nutr Hosp 2014;29:94-101.
26. Perumpail BJ, Cholankeril R, Yoo ER, Kim D, Ahmed A. An Overview of Dietary Interventions and Strategies to Optimize the Management of Non-Alcoholic Fatty Liver Disease. Diseases 2017;5:E23
27. Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD, *et al*. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. N Engl J Med 2009;360:859-73.

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