Effects of low-carbohydrate vs low-fat diets on weight loss and metabolic risk factors in obese/overweight individuals with impaired glucose regulation: a randomized controlled trial

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Running title: Low-carb diet vs low-fat diet on prediabetes

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ABSTRACT

Background and Objectives: The aim of this study was to compare the effects of low-carbohydrate diet (LCD) versus low-fat diet (LFD) on weight loss, glycemic control and metabolic risk factors in individuals with impaired glucose regulation (IGR) after 10-week intervention. **Methods and Study Design:** In this 10-week randomized controlled trial, 90 obese/overweight adults with IGR were randomly assigned to consume either low-carbohydrate diet (20%-25% energy from carbohydrates, 30%-45% energy from fat, 40%-45% energy from protein), or low-fat diet (40%-55% energy from carbohydrates, 20%-30% energy from fat, 20%-30% energy from protein), or heath education (HE) group. The anthropometry and body composition were collected at baseline, week 4, week 8 and week 10. The glycemia and metabolic indicators were assessed at baseline and week 10. **Results:** A total of 69 participants (mean±SE age: 39.2±1.0 years, 72.5% women) completed the intervention and were included in the final analysis. At week 10, all three groups presented similar mean reduction in weight (LCD: 5.80±0.6 kg; LFD: 6.36±0.57kg; HE: 4.49±0.98 kg), and fasting blood glucose (LCD: 0.73±0.13 mmol/L; LFD: 0.84±0.17 mmol/L; HE: 0.58±0.14 mmol/L). Additionally, there were no differences in the improvements of TG and liver function markers between diets, the low-fat diet exhibited more favorable effects on TC level. **Conclusions:** Both diets achieved similar weight loss, fasting glucose, and insulin reduction in short-term, suggesting each diet pattern could be an effective strategy for the prediabetes management.

Key Words: low-carbohydrate diet, low-fat diet, overweight, obesity, impaired glucose regulation

INTRODUCTION

According to the 10th International Diabetes Federation, the prevalence of diabetes is 537 million (10.5%) in 2021, and this number is predicted to reach 643 million (11.3%) by 2030 and 783 million (12.2%) by 2045. China is considered to be the largest number of adults with diabetes and the number is 140.9 million in 2021.[1] The most common type of diabetes, T2DM is accounted for over 90% of all diabetes worldwide. Due to the exact time of the onset of T2DM is indeterminate, there is usually a long pre-diagnostic period and as many as one-third to one-half of people with T2DM in population may be undiagnosed. Diabetic complications such as retinopathy, lower-limb ulcers, nerve damage, kidney damage and cardiovascular disease may lead to the diagnosis.[2,3] As a result, the detection of prediabetes or intermediate

hyperglycemia can open the door to interventions that can lead to the prevention of T2DM. Impaired glucose regulation (IGR), defined by the American Diabetes Association (ADA), including impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or elevated glycated hemoglobin (HbA1c), is recognized as being a stage in the transition from normality to diabetes. The causes of T2DM are not fully illustrated but there is a strong link with overweight, obesity, less physical activity, behavior and diet.[4,5]

The problem of obesity has become increasingly prominent worldwide. The Report on Nutrition and Chronic Diseases of Chinese Residents (2020) shows the rates of overweight and obesity among residents aged 18 and over have risen to 34.3% and 16.4%, respectively.[6] Obesity has increased the incidence of cardiovascular disease (CVD), type 2 diabetes, cancer, and all-cause mortality.[7,8] Strong evidence from large randomized, controlled trials (RCTs) and meta-analyses demonstrated that for individuals with IGR, lifestyle modification is effective in producing reductions in progression to diabetes.[9-11] These lifestyle modifications generally focus on weight reduction by modifying dietary patterns, physical activity, and other health-related behaviors.

Although a wide variety of researches have reported that traditional dietary guidelines (low fat, high-carbohydrate, reduced-calorie diets; [LFD]) was an effective method for promoting weight loss and may improve metabolic effects in overweight and obese individuals, emerging evidence have supported that compared with low fat diet, low-carbohydrate diet (LCD) may have more advantages.[12,13] Previous meta-analysis has revealed that compared to LFD, LCD have exerted greater effects on weight loss, triglycerides, high-density lipoprotein cholesterol (HDL-C) and blood pressure.[12] However, studies involving LCD focused on IGR population are limited. Previous randomized trials were conducted among T2DM or prediabetes and revealed participants assigned to a very low carbohydrate diet may have greater reductions in HbA1c, lose more weight and even decrease more diabetes medication. While, the participants with prediabetes were very less and only four prediabetes were included.[14,15] Although recent studies have investigated the associations of LCD and LFD with mortality among individuals with prediabetes and found that lower carbohydrate intake or healthy LCD scores was associated with a lower all-cause mortality rate in people with prediabetes, these researches only focused on the risk of mortality.[16,17] Yet, it is difficult to evaluate whether LCD is more suitable for adults with prediabetes. Therefore, it is necessary to provide further evidence regarding the effects of LCD on weight loss, glycemic control, anthropometric index and other metabolic index. Therefore, this RCT is conducted to assess the effect of LCD and LFD on weight loss and metabolic risk factors and assess whether LCD

or LFD would have additional benefits in terms of these outcomes among prediabetes population.

MATERIALS AND METHODS

Study design and eligibility

This study was a multicenter, randomized controlled trial done at six clinical centers in the Zhejiang province, China. Eligible trial participants were randomly assigned to LFD group, LCD group and health education (HE) group for 10 weeks. Participant enrollment began on May 2020, and continued through July, 2021. All the participants provided written informed consent. The protocol was approved by the Human Subject Research Ethics Committee, the Second Affiliated Hospital, Zhejiang University School of Medicine. Trial Registration: ClinicalTrials.gov number, NCT04469400.

IGR was defined as IFG or/and IGT based on the ADA criteria.[18] The criteria for eligibility were as following, age of 30 to 65 years, BMI of 24-35 kg/m^2, FBG of 5.6-6.9 mmol/L or oral glucose tolerance test (OGTT) 2h plasma glucose (2h-PBG) of 7.8-11.1 mmol/L. The the criteria for exclusion were individuals diagnosed diabetes or receive the diabetes treatment, current or received weight-loss treatment/surgery within 3 months before randomization, receiving corticosteroids or thyroid hormones, serious liver dysfunction or chronic kidney disease, having gastro-intestinal problems that effect digestion and absorption, suffering infectious diseases, and being pregnant or lactating.

Intervention programs

During the 10 weeks of the trial, three groups were instructed to follow the diet with restricted energy: initial bodyweight × 25 kcal/kg × 0.7, but not less than 1000 kcal/d for women and 1200 kcal/d for men. The calorie-restricted formula was based on the Consensus of Experts on Medical Nutrition Therapy for Overweight/Obesity in China (2016)19. Participants in LFD group were instructed to follow the traditional balanced diet/low-fat diet (40-55% energy from carbohydrates, 20-30% energy from protein, 20-30% energy from fat), provided with protein shake two servings per day (one serving: 108 kcal: 7.3g carbohydrate, 14.4g protein, and 1.8g fat; Nutriease Health Technology Co, Ltd., Hangzhou, China) to increase satiety and help improve adherence to the permitted calorie intake. LCD group was instructed to follow the low-carbohydrate diet (20-25% energy from carbohydrates, 40-45% energy from protein,30-45% energy from fat), provided with the nutrition bar two servings per day (one serving: 186 kcal, 15.8g carbohydrate, 17.2g protein, and 7.9g fat; Nutriease Health

Technology Co, Ltd., Hangzhou, China) to reduce the carbohydrate intake and ensure adequate intake of essential nutrients. Participants in HE group were constructed to follow traditional balanced diet with detailed instruction. During the intervention, all participants were encouraged to participate in at least 150 minutes of moderate-intensity aerobic activity and 2-3 resistance exercises per week, to record their daily diet and exercise activities on the online platform. In addition, participants received follow-up telephone calls or messages per week for lifestyle guidance and dietary counseling.

Assessments

Information on demographic characteristics, socioeconomic status, lifestyle behaviors and physical activity levels was collected using a standard questionnaire at baseline. Anthropometric measurements were performed at baseline, week 4, week 8 and week 10 on an outpatient basis. Height and weight were measured using a stadiometer and a periodically calibrated scale accurate to 0.1 kg, respectively. Body fat mass (BF), body fat percentage (BFP), visceral fat area (VFA), BMR were assessed using bioelectrical impedance analysis by Inbody720 (InBody, Seoul, Korea). Waist circumference was measured at the mid-point between the lowest rib and the iliac crest after inhalation and exhalation, while hip circumference was measured at the widest girth of the hip. Plasma concentrations of fasting blood glucose (FBG) and 2-h blood glucose (PBG), insulin, HbA1c, triglycerides (TG), total cholesterol(TC), high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C), alanine aminotransferase (ALT), aspartic transaminase (AST), γ-glutamyl transferase (GGT), creatinine, urea N (UN) and uric acid (UA) were measured by blood sample obtained by venipuncture after an overnight fasting at baseline and week 10. HOMA-IR was calculated with the following: fasting serum insulin (μU/ml) + fasting plasma glucose (mmol/l)/22.5.[20]

Statistical analysis

All continuous variables were tested for normal distribution by the Kolmogorov–Smirnov normality test. Within-group differences were analyzed using paired t tests for variables with normal distribution or Wilcoxon–Mann–Whitney rank-sum tests for those skewed variables. To evaluate the repeated measurements of weight and body composition over time, we used generalized estimating equations for panel data analysis. Between-group differences for changes in metabolic biomarkers were evaluated using generalized linear models. The association between change in weight and metabolic risk factors were assessed by generalized

linear models. All models were adjusted for age, BMI, married age, gender, education, married status, smoking status, alcohol consumption. Data were presented as mean ± SE. *p* values <0.05 (2-tailed tests) were statistically significant. Statistical analysis was performed using STATA version 15.1 (Stata Corporation, College Station, TX, USA).

RESULTS

A total of 69 trial participants were included in current analysis. Twenty-one participants dropped out before completing the study (Figure 1). The baseline characteristics of included individuals are shown in Table 1. The mean age was 39.2±0.96 years, most participants were women (72.5%) and college degree (75.4%). Overall, 60.86% of participants were obesity, the mean weight was 78.8±1.50 kg, and the mean BFP was 36.1±0.54. No significant differences in baseline characteristics were observed among the groups.

The changes of anthropometry and body compositions at week 4, week 8 and week 10 are presented in Figure 2. All three groups reported significant decrease in weight compared with baseline (p<0.001). The overall weight changes during the 10-week intervention were 5.78±0.60kg for the LCD group, 6.36±0.57 kg for LFD and 4.49±0.98 kg for the HE. While there was no statistically difference among groups (p>0.05). The mean changes in BMI were 2.28±0.24 kg/m^2 in the LCD group,1.66±0.35 kg/m^2 in the LFD group, and 2.36±0.20 kg/m^2 in the HE group (p>0.05 for the comparison among groups). All groups had significant decreases in BF, BFP and VFA (p<0.001). The BF and BFP decreased by a mean of 5.61±1.04 kg and 3.75±0.59% in the LCD group, 5.22±0.51 kg and 3.47±0.64% in the LFD group, 3.25±0.82 kg and 2.34±0.66% in the HE group. VFA fell by 22.43±3.05 cm^2 in the LCD group, 23.62±2.82 cm^2 in the LFD group, and 9.89±6.35 cm^2 in the HE group (p>0.05 for the comparison among groups).

The changes in metabolic risk factors by diet group are shown in Table 2. There were significant decreases in FPG level in all groups at 10 weeks, with no significant differences observed among the groups in the amount of improvement. The level of 2h-PBG only decreased in HE group. A total of 56.5% of participants had reverted to the normoglycemic state (FBG level <5.6 mmol/L or 2h-PBG <7.8 mmol/L), no substantial differences in the rate among groups. The improvement of fasting plasma insulin was observed in LFD and LCD group, but the reduction of HOMA-IR was observed in all three groups. The changes in HOMA-IR were not different among groups. More individuals with elevated Hb1Ac levels in LCD group had reached to normal HAb1c level compared to LFD, though there were no significant difference in HAb1c change in all groups.

The TG level was significantly reduced from baseline to 10 weeks in three groups with no significant differences in the amount of reduction among groups. The TC level was significant decreased in LFD and HE group, while the LDL-C level only decreased in HE group. In addition, HDL-C levels did not change significantly within groups, the ratio of TC to HDL-C was decreased only in LCD group. LFD had more favorable effect on TC reduction (p=0.038). The changes of GGT, ALT and AST level were significant in three groups, with no substantial differences among groups. The UA level was significantly decreased in LFD and HE group. In addition, plasma urea level significantly increased in LCD group.

The associations of weight change with metabolic indices are shown in Table 3. Weight change at week 10 was associated with FPG reduction, while were not associated with insulin change. As for the liver function tests, the significant association of weight change with GGT, ALT and AST reduction was observed.

DISCUSSION

In this randomized controlled 10-week trial, our results showed the LCD and LFD were effective in short-term weight loss, FBG and insulin improvement in obese/overweight adults with IGR. In addition, LCD and LFD had similar beneficial effects in insulin, HOMA-IR, TG and liver function markers, while LFD exhibited more favorable effects on TC level. Furthermore, we found the change of weight was significantly associated with the reduction of FPG and liver function indicators.

Several studies have previously compared the effectiveness of LCD and LFD on glycemia among individuals with T2DM. Recent systematic reviews and meta-analysis among people with T2DM showed LCD achieved greater reductions in HbA1c and FBG compared with LCD intervention ≥ 12 weeks or medium term (≥8-16 weeks and ≥16-26 weeks) follow-up.[21,22] The relative short intervention (10 weeks) might explain no significant difference in the improvement of HbA1c and FBG between the two groups in our study. In other term, restrictions of carbohydrate have been variably in these studies, the dose-response meta-analysis further demonstrated the HbA1c and FPG decreased linearly with the decrease in carbohydrate intake from 65% to 10%.[23] The carbohydrate proportion in our study was restricted to 20-25%, might be less effective in improving glycemia.

Existing evidence on changes in weight and body composition in response to LCD and LFD diets remains highly heterogeneous.[24-26] We found the participants in LCD and LFD group had significant and similar decrease in weight, BF, BFP and VFA. These findings were consistent with the results of some previous studies.[27-30] Another meta-analysis of trials

among overweight/obesity adults demonstrated LCD (carbohydrate < 20%) had greater effect on weight loss, but similar effect on fat mass change compared with LFD.[31] But not all trials report significant differences in weight loss between the LCD and LFD. It was noted that the effect of LCD and LFD on weight loss might have gender differences. The secondary analysis of the Diet Intervention Examining the Factors Interacting with Treatment Success trial (DIETFITS) showed LCD produced greater weight loss and fat mass than LFD among males, but not among females.[32] The sample in our study consisted of mostly females (72.46%), which is too small for subgroup analyses by gender. Further studies need focus on gender difference when comparing different diets effect on weight loss.

Within our study, the lipid profiles, liver and renal function markers improvements were not observed in all groups. The TC level significant decreased only in LFD, which were in line with previous studies.[33] In addition, LDL-C is an important risk factor for cardiovascular disease, the impact of LCD on LDL-C level is heavily debated. While some systematic reviews and meta-analyses show that LCD increase levels of this lipoprotein, other show reductions or no change.[12,26,27,34] The short-term LCD in our study did not lead to the similar unfavorable effect. The improvements of liver function markers were also observed in other studies. In addition, the urea N increased in LCD group might be due to increased protein take.

Research focused on the glycemic effects of LCD among individuals with prediabetes is very limited. There are only few pilot studies performed in prediabetes found that the LCD and very low-carbohydrate diet led to improvement of HbA1c and other glycemic outcomes.[35-37] We found that individuals with IGR could achieve remission through a short-term intervention, and the FBG or 2-hPBG level of 46 participants (66.67%) has turned to normal. Furthermore, 57.97% of participants had reached the 7% weight loss goal that recommended by ADA for prediabetes.[38]

The present study has several limitations. Firstly, the drop-out rate is relatively high, especially in HE group. This may be due to preference for a specific intervention of participants. Secondly, daily diet and physical activity data were recorded by participants themselves on the online platform, the validity of records might be compromised. Finally, being a short-term designed study, the evidence of the longer effects of LCD on prediabetes was unclear. We are still following the participants for 1-year clinical effects, the results will be published in a future study.

It is worth noting that HE also had favorable reduction on glycemia and metabolic risk factors. The diet construction of HE group was similar to LCD, but drop-out rate in this group was quite high, which may result that the individuals with better compliance were included in

analysis. Participants in LCD group and LFD group are easier to adhere the constructed diet with the use of convenient food. In our point of view, each type of diet featuring weight loss if it is well accepted is effective in weight control when nutritional support by professionals is guaranteed. Metabolic improvements from short-term weight loss were not affected by diet type. Further studies are needed to be designed to investigate the longer-term effects.

Conclusion

In conclusion, both LCD and LFD produced comparable weight loss and improvement in FBG, insulin and several metabolic risk factors. The decrease in TG was observed in all groups, but decrease in TC was only observed in LFD group. The change of weight was significantly associated with the reduction of FPG and liver function indicators. These results suggest that both LCD and LFD could be viable management strategy for prediabetes.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare no conflict of interest.

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REFERENCES

1. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022;183:109119. doi: 10.1016/j.diabres.2021.109119.
2. Ramasamy R, Shekhtman A, Schmidt AM. The RAGE/DIAPH1 Signaling axis & implications for the pathogenesis of diabetic complications. Int J Mol Sci. 2022;23:4579. doi: 10.3390/ijms23094579.
3. Mekonen EG, Gebeyehu Demssie T. Preventive foot self-care practice and associated factors among diabetic patients attending the university of Gondar comprehensive specialized referral hospital, Northwest Ethiopia, 2021. BMC Endoc Disord. 2022;22:124. doi: 10.1186/s12902-022-01044-0.
4. Huang S, Shi K, Ren Y, Wang J, Yan W-F, Qian W-L, Yang Z-G, Li Y. Association of magnitude of weight loss and weight variability with mortality and major cardiovascular events among individuals with type 2 diabetes mellitus: a systematic review and meta-analysis. Cardiovas Diabetol. 2022;21:78. doi: 10.1186/s12933-022-01503-x.

5. Sarsangi P, Salehi-Abargouei A, Ebrahimpour-Koujan S, Esmaillzadeh A. Association between adherence to the Mediterranean diet and risk of type 2 diabetes: An updated systematic review and dose-response meta-analysis of prospective cohort studies. Adv Nutr. 2022;nmac046. doi: 10.1093/advances/nmac046.
6. Report on Nutrition and chronic Diseases of Chinese residents. Acta Nutrimenta Sinica. 2020;42:521.
7. Jayedi A, Soltani S, Motlagh SZ-t, Emadi A, Shahinfar H, Moosavi H, Shab-Bidar S. Anthropometric and adiposity indicators and risk of type 2 diabetes: systematic review and dose-response meta-analysis of cohort studies. BMJ. 2022;376:e067516. doi:10.1136/bmj-2021-067516.
8. Tarp J, Grøntved A, Sanchez‐Lastra MA, Dalene KE, Ding D, Ekelund U. Fitness, fatness, and mortality in men and women from the UK Biobank: prospective cohort study. J Am Heart Assoc. 2021;10:e019605. doi: 10.1161/JAHA.120.019605.
9. Group DPPR. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet. 2009;374:1677-86. doi: 10.1016/S0140-6736(09)61457-4.
10. Jiang Q, Li J-T, Sun P, Wang L-L, Sun L-Z, Pang S-G. Effects of lifestyle interventions on glucose regulation and diabetes risk in adults with impaired glucose tolerance or prediabetes: a meta-analysis. Arch Endocrinol Metab. 2022.66:157-67. doi: 10.20945/2359-3997000000441.
11. Li G, Zhang P, Wang J, An Y, Gong Q, Gregg EW et al. Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing Diabetes Prevention Study: a 23-year follow-up study. Lancet Diabetes Endocrinol. 2014;2:474-80. doi: 10.1016/S2213-8587(14)70057-9.
12. Bueno NB, de Melo ISV, de Oliveira SL, da Rocha Ataide T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. British Journal of Nutrition. 2013;110:1178-87. doi: 10.1017/S0007114513000548
13. Sun J, Xu N, Lin N, Wu P, Yuan K, An S et al. 317-LB: optimal weight loss effect of short-term low carbohydrate diet with calorie restriction on overweight/obese subjects in South China—a multicenter randomized controlled trial. Diabetes. 2019;68. doi: 10.2337/db19-317-LB.
14. Saslow LR, Kim S, Daubenmier JJ, Moskowitz JT, Phinney SD, Goldman V et al. A randomized pilot trial of a moderate carbohydrate diet compared to a very low carbohydrate diet in overweight or obese individuals with type 2 diabetes mellitus or prediabetes. PLoS One. 2014;9:e91027. doi: 10.1371/journal.pone.0091027.
15. Saslow LR, Daubenmier JJ, Moskowitz JT, Kim S, Murphy EJ, Phinney SD et al. Twelve-month outcomes of a randomized trial of a moderate-carbohydrate versus very low-carbohydrate diet in overweight adults with type 2 diabetes mellitus or prediabetes. Nutrition & Diabetes. 2017;7:1-6. doi: 10.1038/s41387-017-0006-9.
16. Lee C-L, Liu W-J, Wang J-S. Associations of low-carbohydrate and low-fat intakes with all-cause mortality in subjects with prediabetes with and without insulin resistance. Clin Nutr. 2021;40:3601-7. doi: 10.1016/j.clnu.2020.12.019.

17. Li L, Shan Z, Wan Z, Li R, Geng T, Lu Q et al. Associations of lower-carbohydrate and lower-fat diets with mortality among people with prediabetes. Am J Clin Nutr. 2022;116:205-15. doi: 10.1093/ajcn/nqac058.
18. Association AD. 2. Classification and diagnosis of diabetes: Standards of medical care in diabetes—2020. Diabetes Care. 2019;43:S14-S31. doi: 10.2337/dc20-S002.
19. Chinese experts consensus compilation committee of medical nutrition treatment for overweight and obesity,Expert consensus on medical nutrition treatment for overweight/obesity in China (2016 edition). Chin J Diabetes Mellitus. 2016;8:540.
20. Matthews DR, Hosker J, Rudenski A, Naylor B, Treacher D, Turner R. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28:412-9. doi: 10.1007/BF00280883.
21. Van Zuuren EJ, Fedorowicz Z, Kuijpers T, Pijl H. Effects of low-carbohydrate-compared with low-fat-diet interventions on metabolic control in people with type 2 diabetes: a systematic review including GRADE assessments. Am J Clin Nutr. 2018;108:300-31. doi: 10.1093/ajcn/nqy096.
22. Goldenberg JZ, Day A, Brinkworth GD, Sato J, Yamada S, Jönsson T et al. Efficacy and safety of low and very low carbohydrate diets for type 2 diabetes remission: systematic review and meta-analysis of published and unpublished randomized trial data. BMJ. 2021;372:m4743. doi: 10.1136/bmj. m4743.
23. Jayedi A, Zeraattalab-Motlagh S, Jabbarzadeh B, Hosseini Y, Jibril AT, Shahinfar H, Mirrafiei A, Hosseini F, Bidar SS. Dose-dependent effect of carbohydrate restriction for type 2 diabetes management: a systematic review and dose-response meta-analysis of randomized controlled trials. Am J Clin Nutr. 2022;116:40-56. doi: 10.1093/ajcn/nqac066.
24. Hashimoto Y, Fukuda T, Oyabu C, Tanaka M, Asano M, Yamazaki M, Fukui M. Impact of low‐carbohydrate diet on body composition: meta‐analysis of randomized controlled studies. Obes Rev. 2016;17:499-509. doi: 10.1111/obr.12405.
25. Al Aamri KS, Alrawahi AH, Al Busaidi N, Al Githi MS, Al Jabri K, Al Balushi F, Ronquillo-Talara R, Al Balushi S, Waly M. The effect of low-carbohydrate ketogenic diet in the management of obesity compared with low caloric, low-fat diet. Clin Nutr ESPEN. 2022;49:522-8. doi: 10.1016/ j.clnesp.2022.02.110.
26. Mansoor N, Vinknes KJ, Veierød MB, Retterstøl K. Effects of low-carbohydrate diets v. low-fat diets on body weight and cardiovascular risk factors: a meta-analysis of randomised controlled trials. Br J Nutr. 2016;115:466-79. doi:10.1017/S0007114515 004699.
27. Hu T, Mills KT, Yao L, Demanelis K, Eloustaz M, Yancy Jr WS, Kelly TN, He J, Bazzano LA. Effects of low-carbohydrate diets versus low-fat diets on metabolic risk factors: a meta-analysis of randomized controlled clinical trials. Am J Epidemiol. 2012;176:S44-S54. doi: 10.1093/aje/kws264.
28. Gardner CD, Trepanowski JF, Del Gobbo LC, Hauser ME, Rigdon J, Ioannidis JP, Desai M, King AC. Effect of low-fat vs low-carbohydrate diet on 12-month weight loss in overweight adults and the association with genotype pattern or insulin secretion: the DIETFITS randomized clinical trial. JAMA. 2018;319:667-79. doi: 10.1001/jama.2018.0245.

29. Frisch S, Zittermann A, Berthold HK, Götting C, Kuhn J, Kleesiek K, Stehle P, Körtke H. A randomized controlled trial on the efficacy of carbohydrate-reduced or fat-reduced diets in patients attending a telemedically guided weight loss program. Cardiovas Diabetol. 2009;8:1-10. doi: 10.1186/1475-2840-8-36
30. Tay J, Luscombe-Marsh ND, Thompson CH, Noakes M, Buckley JD, Wittert GA, Yancy Jr WS, Brinkworth GD. Comparison of low-and high-carbohydrate diets for type 2 diabetes management: a randomized trial. Am J Clin Nutr. 2015;102:780-90. doi: 10.3945/ajcn.115.112581.
31. Yang Q, Lang X, Li W, Liang Y. The effects of low-fat, high-carbohydrate diets vs. low-carbohydrate, high-fat diets on weight, blood pressure, serum liquids and blood glucose: a systematic review and meta-analysis. Eur J Clin Nutr. 2021;76:16-27. doi: 10.1038/s41430-021-00927-0.
32. Aronica L, Rigdon J, Offringa LC, Stefanick ML, Gardner CD. Examining differences between overweight women and men in 12-month weight loss study comparing healthy low-carbohydrate vs. low-fat diets. Int J Obes. 2021;45:225-34. doi: 10.1038/s41366-020-00708-y.
33. Chawla S, Tessarolo Silva F, Amaral Medeiros S, Mekary RA, Radenkovic D. The effect of low-fat and low-carbohydrate diets on weight loss and lipid levels: a systematic review and meta-analysis. Nutrients. 2020;12:3774. doi: 10.3390/nu12123774.
34. Gjuladin-Hellon T, Davies IG, Penson P, Amiri Baghbadorani R. Effects of carbohydrate-restricted diets on low-density lipoprotein cholesterol levels in overweight and obese adults: a systematic review and meta-analysis. Nutr Rev. 2019;77:161-80. doi: 10.1093/nutrit/ nuy049.
35. Maekawa S, Kawahara T, Nomura R, Murase T, Ann Y, Oeholm M, Harada M. Retrospective study on the efficacy of a low-carbohydrate diet for impaired glucose tolerance. Diabetes Metab Syndr Obes. 2014;7:195. doi: 10.2147/DMSO.S62681.
36. Griauzde DH, Saslow L, Patterson K, Ansari T, Liestenfeltz B, Tisack A, Bihn P, Shopinski S, Richardson CR. Mixed methods pilot study of a low-carbohydrate diabetes prevention programme among adults with pre-diabetes in the USA. BMJ Open. 2020;10:e033397. doi: 10.1136/bmjopen-2019-033397.
37. Dorans KS, Bazzano LA, Qi L, He H, Appel LJ, Samet JM et al. Low-carbohydrate dietary pattern on glycemic outcomes trial (ADEPT) among individuals with elevated hemoglobin A1c: study protocol for a randomized controlled trial. Trials. 2021;22:1-12. doi: 10.1186/s13063-020-05001-x.
38. Association AD. 3. Prevention or delay of type 2 diabetes: Standards of Medical Care in Diabetes—2020. Diabetes Care. 2020;43:S32-S6. doi: 10.2337/dc20-S003.

Table 1. Baseline characteristics of study participants

Baseline characteristic	Low-carbohydrate diet group (n=27)	Low-fat diet group (n=24)	Heath education group (n=18)	*p*
Age (years)	38.30±1.71	41.33 ±1.41	37.89 ±1.83	0.38
Male	6 (22.2%)	8 (33.3%)	5 (27.8%)	0.675
Body weight	77.58±2.46	79.46±2.32	79.9±3.26	0.6536
BMI	29.22±0.60	28.93±2.98	29.85±0.78	0.4014
Body composition				
Body fat (kg)	29.64±1.46	28.00±1.22	29.78±1.56	0.2898
Muscle mass (kg)	45.55±1.26	48.11±1.70	46.81±1.98	0.5792
Body fat percentage (%)	36.71±0.72	34.64±1.03	37.15±1.00	0.6856
Visceral fat area (cm^2)	119.84±29.40	120.3±6.12	132.2±7.27	0.5392
Basic metabolic rate (kcal)	1394.59±34.45	1485.17±48.34	1445.61±50.98	0.376
Education				
High school	0 (0%)	1 (4.17%)	1(5.56%)	0.493
College	22 (81.48%)	16 (66.67%)	14(77.78%)	
Graduate degree	1 (3.7%)	1 (4.17%)	2(11.11%)	
Others	4 (14.81%)	6 (25.00%)	1(5.56%)	
Married	24 (88.89%)	22 (91.67%)	15 (83.33%)	0.702
Smoking	2 (7.41%)	5 (20.83%)	3 (16.67%)	0.379
Alcohol drinking	2 (7.41%)	5 (20.83%)	1 (5.56%)	0.212

Values are presented as mean ± standard error of mean.

Table 2. Changes in metabolic risk factors

Variables	Intervention group					
	Low-carbohydrate diet		Low-fat diet		Heath education	
	Baseline	Week 10	Baseline	Week 10	Baseline	Week 10
Glycemic control indicators						
Fasting blood glucose (mmol/L)	5.98 (0.08)	5.18 (0.14) **	6.08 (0.11)	5.45 (0.11) **	5.89 (0.12)	5.13 (0.16) **
2-h postprandial blood glucose (mmol/L)	6.88 (0.34)	6.53 (0.32)	7.17 (0.35)	6.55 (0.33)	7.54 (0.41)	6.27 (0.38) **
Insulin (pmol/L)	67.40 (10.9)	54.09 (8.97) *	60.64 (13.00)	39.13 (7.07) **	70.55 (19.11)	61.03 (18.93)
HbA1c(%)	5.57 (0.10)	5.45 (0.08)	6.00 (0.15)	5.79 (0.36)	5.73 (0.16)	5.52 (0.12)
HOMA-IR	2.60 (0.44)	1.86 (0.34) **	2.40 (0.53)	1.39 (0.26) **	2.72 (0.78)	2.01 (0.63) *
Lipid profiles						
Triglycerides (mmol/L)	1.70 (0.19)	1.42 (0.32) **	1.93 (0.25)	1.29 (0.18) **	2.24 (0.33)	1.70 (0.17) **
Total cholesterol(mmol/L)	4.82 (0.21)	4.79 (0.20)	5.32 (0.23)	4.60 (0.28) **	5.64 (0.27)	5.21 (0.34) **
LDL-cholesterol (mmol/L)	2.98 (0.16)	2.93 (0.16)	3.15 (0.19)	2.87 (0.20)	3.62 (0.27)	3.27 (0.26) **
HDL-cholesterol (mmol/L)	1.23 (0.04)	1.26 (0.05)	1.26 (0.94)	1.23 (0.94)	1.31 (0.09)	1.20 (0.62)
Total cholesterol to HDL-cholesterol ratio	4.07 (0.21)	3.92 (0.19)	4.67 (0.38)	3.93 (0.27) **	4.51 (0.31)	4.42 (0.26)
Liver and renal function markers						
Gamma-glutamyl transferase (U/L)	45.94 (9.69)	29.65 (3.32) **	41.78 (6.11)	33.27 (6.30) **	48.73 (8.06)	31.01 (3.32) **
Alanine amino transferase (U/L)	45.71 (9.15)	25.87 (4.17) **	53.12 (7.19)	34.95 (8.35) **	57.92 (7.56)	37.43 (6.19) *
Aspartic transaminase (U/L)	28.36 (3.76)	20.71 (2.17) *	34.01 (3.45)	24.94 (2.70) **	41.87 (9.25)	23.04 (2.34) **
Creatine (μmol)	58.73 (1.74)	59.43 (2.14)	64.15 (3.16)	63.08 (2.71)	58.86 (3.18)	61.62 (2.78)
Uric acid (μmol)	356.09 (23.28)	332.63 (13.98)	371.11 (13.80)	346.54 (13.00) *	385.5 (24.24)	348.9 (19.93) *
Urea N (mmol/L)	4.41 (0.18)	4.84 (0.18) **	4.94 (0.23)	5.32 (0.28)	4.75 (0.34)	4.44 (0.29)

HbA1c: glycated hemoglobin.
Values are presented as mean (standard error of mean).
*p<0.05 and **p<0.01 for paired t tests or Wilcoxon–Mann–Whitney rank-sum tests .

Table 3. Relation between change in weight and metabolic outcomes: generalized linear models[†]

Variables	Intervention group					
	Low-carbohydrate diet		Low-fat diet `		Heath education	
	Baseline	Week 10	Baseline	Week 10	Baseline	Week 10
Glycemic control indicators						
Fasting blood glucose (mmol/L)	5.98 (0.08)	5.18 (0.14) **	6.08 (0.11)	5.45 (0.11) **	5.89 (0.12)	5.13 (0.16) **
2-h postprandial blood glucose (mmol/L)	6.88 (0.34)	6.53 (0.32)	7.17 (0.35)	6.55 (0.33)	7.54 (0.41)	6.27 (0.38) **
Insulin (pmol/L)	67.40 (10.9)	54.09 (8.97) *	60.64 (13.00)	39.13 (7.07) **	70.55 (19.11)	61.03 (18.93)
HbA1c(%)	5.57 (0.10)	5.45 (0.08)	6.00 (0.15)	5.79 (0.36)	5.73 (0.16)	5.52 (0.12)
HOMA-IR	2.60 (0.44)	1.86 (0.34) **	2.40 (0.53)	1.39 (0.26) **	2.72 (0.78)	2.01 (0.63) *
Lipid profiles						
Triglycerides (mmol/L)	1.70 (0.19)	1.42 (0.32) **	1.93 (0.25)	1.29 (0.18) **	2.24 (0.33)	1.70 (0.17) **
Total cholesterol(mmol/L)	4.82 (0.21)	4.79 (0.20)	5.32 (0.23)	4.60 (0.28) **	5.64 (0.27)	5.21 (0.34) **
LDL-cholesterol (mmol/L)	2.98 (0.16)	2.93 (0.16)	3.15 (0.19)	2.87 (0.20)	3.62 (0.27)	3.27 (0.26) **
HDL-cholesterol (mmol/L)	1.23 (0.04)	1.26 (0.05)	1.26 (0.94)	1.23 (0.94)	1.31 (0.09)	1.20 (0.62)
Total cholesterol to HDL-cholesterol ratio	4.07 (0.21)	3.92 (0.19)	4.67 (0.38)	3.93 (0.27) **	4.51 (0.31)	4.42 (0.26)
Liver and renal function markers						
Gamma-glutamyl transferase (U/L)	45.94 (9.69)	29.65 (3.32) **	41.78 (6.11)	33.27 (6.30) **	48.73 (8.06)	31.01 (3.32) **
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Creatine (μmol)	58.73 (1.74)	59.43 (2.14)	64.15 (3.16)	63.08 (2.71)	58.86 (3.18)	61.62 (2.78)
Uric acid (μmol)	356.09 (23.28)	332.63 (13.98)	371.11 (13.80)	346.54 (13.00) *	385.5 (24.24)	348.9 (19.93) *
Urea N (mmol/L)	4.41 (0.18)	4.84 (0.18) **	4.94 (0.23)	5.32 (0.28)	4.75 (0.34)	4.44 (0.29)

FBG: fasting blood glucose; HbA1c: glycated hemoglobin; GGT: γ-glutamyl transferase; ALT: alanine aminotransferase; AST: aspartic transaminase.
[†]Generalized regression model was adjusted for age, BMI, gender, education, smoking, married status, alcohol drinking.

Table 3. A comparison of the characteristics of those who had and had not heard of coeliac disease (n=90)

Variables in models	FBG reduction		Insulin reduction		HbA1c reduction		GGT reduction		ALT reduction		AST reduction	
	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
Baseline level	0.73	<0.001	0.35	<0.001	0.61	<0.001	0.38	<0.001	0.75	<0.001	0.84	<0.001
Weight loss at week 10 (kg)	0.06	0.035	2.41	0.060	0.02	0.217	2.10	0.021	3.85	0.002	1.41	0.002
Low fat diet vs. Low carbohydrate diet	-0.24	0.217	7.60	0.392	-0.18	0.072	-5.69	0.361	-8.77	0.288	-3.21	0.295
Health education group vs. Low carbohydrate diet	0.09	0.670	-1.71	0.857	0.03	0.810	2.46	0.712	-2.84	0.745	2.07	0.529

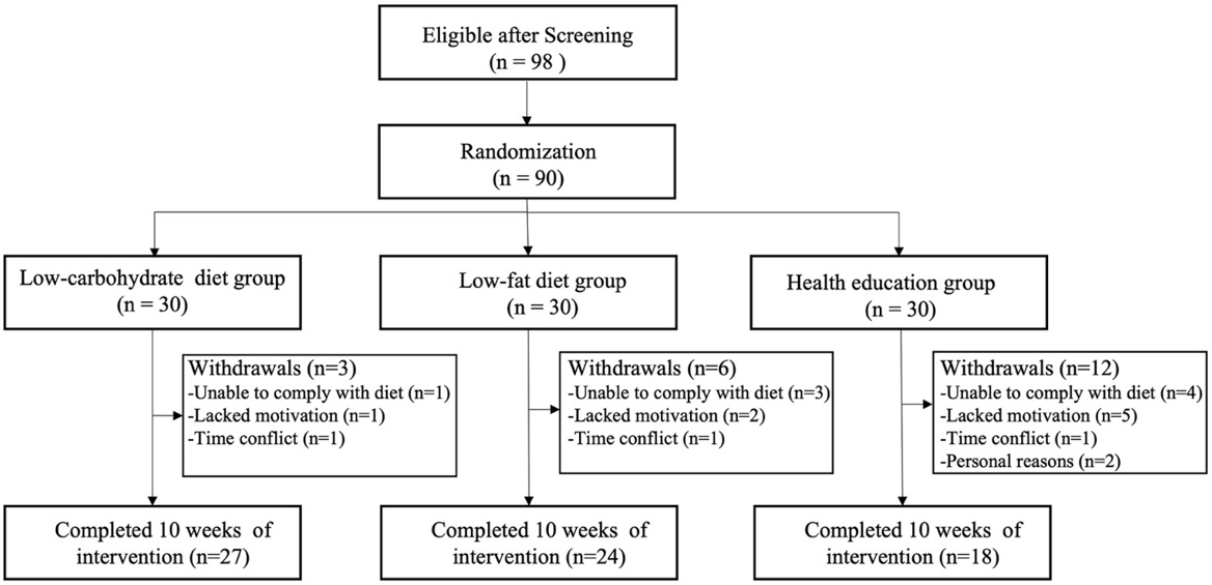

Figure 1. Flowchart of participants through the study.

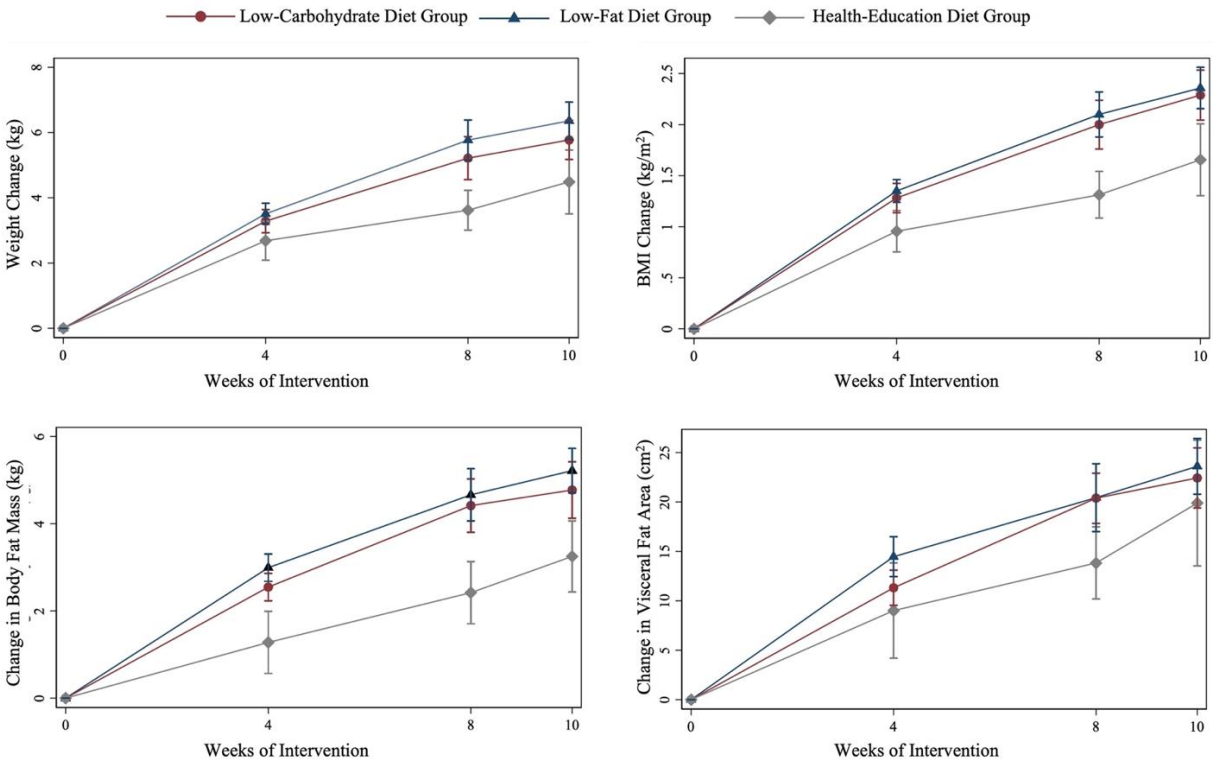

Figure 2. Changes in weight, BMI, body fat mass, visceral fat area during the intervention. Vertical bars indicate SEs.