Emagrecimento CIENTÍFICO | Método 4 FASES

SEM CIRURGIA
SEM REMÉDIO
SEM FOME

Dr. Edson Ramuth

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Miami, 16 febrery 2016

To
AVP Strategic Operations & Business Development
International Medicine Institute
University of Miami

Good Morning,

Please find bellow a brief summary of the scientific papers and a complete scientific research supporting the "Scientific Diet" can be downloaded on: http://downloadsmultifranquias.com.br/METODO 4 FASES/Manuais/Resumo%20-%20Trabalhos%20Cientificos_ingles.rar

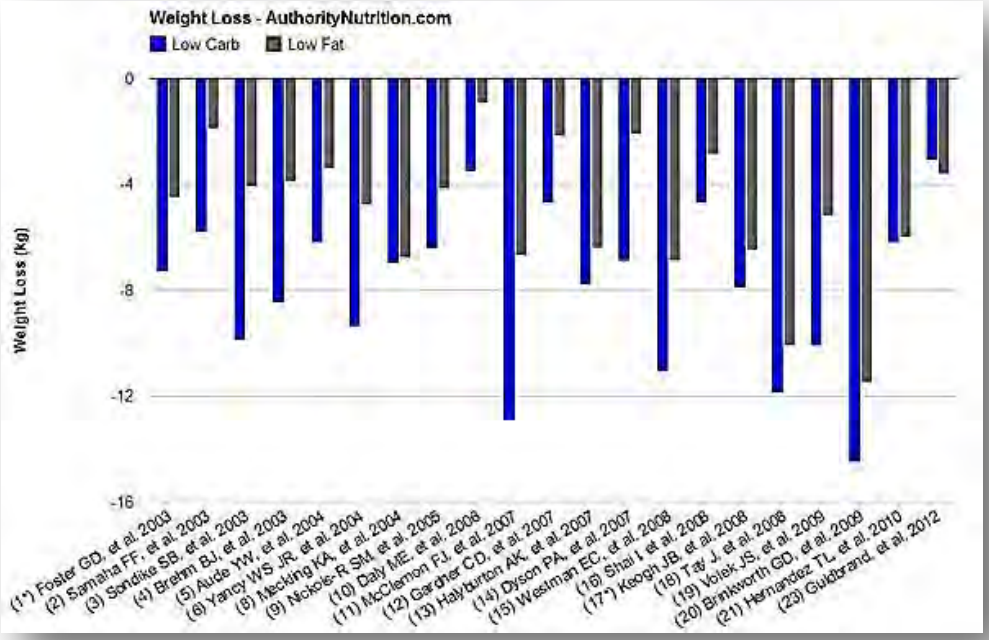
METODO 4 FASES was founded 30 years ago (1986) in Brazil and currently we have over 150 branches spreads in the whole country. Since then, METODO 4 FASES treated almost 1 milhon patients. Currently, approximately 90,000 new patients per year.

With so many patients undergoing our program, we were able to develop specific weight loss treatment that´s being used in the last 5 years: The "Scientific Diet Program".

The "Scientific Diet" is a low-carbohydrate diet that can be followed for a long period with no harm to the patient's health. Actually, studies show that it brings many benefits reducing triglyceride levels, LDL-cholesterol, blood glucose, C-reactive protein and blood pressure and increasing HDL. It doesn't lead to any cardiovascular harm to the patient and it can be prescribed to type 2 diabetic and hypertensive patients..

In the US about 73% of the population is overweight or obese. Treating their comorbidities generates an annual cost of about $ 200 billion.

Virtually all scientific studies shows that low-carbohydrate diets have better results in terms of weight loss than low fat and low calories diets.



About The "Scientific Diet Program":

Our weight-loss treatment has 4 phases and it uses the "Scientific Diet" (a low-carbohydrate diet).

There is a restriction on the intake of carbohydrates. The patient can consume fat and protein at its own discretion, as long as he respect the minimal intake of 0,6 g protein / pound of weight (normal protein); i.e. we can characterize the "Scientific Diet" as a low-carbohydrate and regular protein diet.

Our diet has a large patient compliance and it is easily done because: (i) there is no calorie counting, the patient only have to count the ingested carbohydrates; and (ii) the patient does not feel hungry during the treatment (even without the use of appetite suppressants).

The patient has his hunger reduced for 3 reasons:

1) In our diet there are some types of food that he can eat at ease when he's hungry;
2) Our diet breaks the "hunger – carbohydrate intake – insulin spike – decreased blood sugar – hunger" cycle because it has a minimum stimulus for release of blood insulin and consequently stabilize blood glucose and insulin;
3) After 24-48 hours in our diet, i.e. consuming a reduced amount of carbohydrate, the body begins the production of ketone bodies by fat metabolism, which produces satiety.

Our "Scientific Diet" consists of four phases:

Phase 1 – DETOX (detoxification):
- Duration: 1 week.
- Restriction of 40 grams of carbohydrates per day.
- Proteins – fish, seafood, egg.

Phase 2 – REDOX (quick weight loss):
- Duration: 4 weeks or more, depending on how much weight the patient has to lose (maximum of 24 weeks).
- Restriction of 40 grams of carbohydrates per day.
- Proteins – fish, seafood, egg, white meat and red meat.

Phase 3 – REINDOX (reintroduction of carbohydrates and nutritional education):
- Duration: 4 weeks
- Restriction of 60 grams of carbohydrates per day (reintroduction of carbohydrates, preferably the ones with low glycemic index, ie, complex carbohydrates).
- Proteins – the patient can ingest all types of proteins, at his own discretion.

Phase 4 – BALANCE (maintenance):
- Duration: 16 weeks
- Restriction of 80 grams of carbohydrates per day (preferably low glycemic index carbohydrates).
- Proteins – the patient can ingest all types of proteins, at his own discretion.

In phases 1 and 2 of the "Scientific Diet", supplementation with Potassium, Calcium, Magnesium and multivitamin is necessary.

The patient must ingest a maximum of 2 grams/day of salt and at least 2 liters of water per day.

During our weight-loss treatment the patient must do a weekly urine test in wich it will be dosed his urinary ketosis (the result must be positive for urinary ketosis during phases 1 and 2).

In 5 weeks, the patient who follows properly our treatment loses 10% of his own body weight.

After finishing our 4 phases treatment, the patients can and should follow a balanced diet as recommended by the US Food Guide 2015-2020:

1. Sugar: its intake should represent less than 10% of the total calories consumed per day;
2. Salt: its intake should be less than one teaspoon per day;
3. Dairy: low-fat or soy milk or cheese: three cups per day;
4. Vegetables: 2 to 3 cups per day;
5. Salads: 4-5 cups per day;
6. Proteins: 5 to 6 ounces per day (if beef, low-fat);
7. Grains: 3 to 4 ounces per day (preferably whole grains);
8. Fruits: 1.5 to 2 cups per day;
9. Oils: 5-7 tablespoons per day;
10. Coffee: 3 to 5 cups per day;
11. Physical activity: 30 minutes per day of walking or another aerobic activities.

Regards,

Edson Ramuth MD

16 february 2016

Summary with 29 scientific worksthe low-carbohydrate Diet.

JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

- The Journal of Clinical Endocrinology & Metabolism>
- List of Issues>
- Volume 88, Issue 4>

A Randomized Trial Comparing a Very Low Carbohydrate Diet and a Calorie-Restricted Low Fat Diet on Body Weight and Cardiovascular Risk Factors in Healthy Women

Bonnie J. Brehm, Randy J. Seeley, Stephen R. Daniels, and David A. D'Alessio

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First Published Online: July 02, 2013

Abstract

Untested alternative weight loss diets, such as very low carbohydrate diets, have unsubstantiated efficacy and the potential to adversely affect cardiovascular risk factors. Therefore, we designed a randomized, controlled trial to determine the effects of a very low carbohydrate diet on body composition and cardiovascular risk factors. Subjects were randomized to 6 months of either an *ad libitum* very low carbohydrate diet or a calorie-restricted diet with 30% of the calories as fat. Anthropometric and metabolic measures were assessed at baseline, 3 months, and 6 months. Fifty-three healthy, obese female volunteers (mean body mass index, 33.6 ± 0.3 kg/m^2) were randomized; 42 (79%) completed the trial. Women on both diets reduced calorie consumption by comparable amounts at 3 and 6 months. The very low carbohydrate diet group lost more weight (8.5 ± 1.0 *vs.* 3.9 ± 1.0 kg; $P < 0.001$) and more body fat (4.8 ± 0.67 *vs.* 2.0 ± 0.75 kg; $P < 0.01$) than the low fat diet group. Mean levels of blood pressure, lipids, fasting glucose, and insulin were within normal ranges in both groups at baseline. Although all of these parameters improved over the course of the study, there were no differences observed between the two diet groups at 3 or 6 months. β-Hydroxybutyrate increased significantly in the very low carbohydrate group at 3 months ($P = 0.001$). Based on these data, a very low carbohydrate diet is more effective than a low fat diet for short-term weight loss and, over 6 months, is not associated with deleterious effects on important cardiovascular risk factors in healthy women.

The New England Journal of Medicine

ORIGINAL ARTICLE

A Randomized Trial of a Low-Carbohydrate Diet for Obesity

Gary D. Foster, Ph.D., Holly R. Wyatt, M.D., James O. Hill, Ph.D., Brian G. McGuckin, Ed.M., Carrie Brill, B.S., B. Selma Mohammed, M.D., Ph.D., Philippe O. Szapary, M.D., Daniel J. Rader, M.D., Joel S. Edman, D.Sc., and Samuel Klein, M.D.

N Engl J Med 2003; 348:2082-2090May 22, 2003DOI: 10.1056/NEJMoa022207

BACKGROUND

Despite the popularity of the low-carbohydrate, high-protein, high-fat (Atkins) diet, no randomized, controlled trials have evaluated its efficacy.

METHODS

We conducted a one-year, multicenter, controlled trial involving 63 obese men and women who were randomly assigned to either a low-carbohydrate, high-protein, high-fat diet or a low-calorie, high-carbohydrate, low-fat (conventional) diet. Professional contact was minimal to replicate the approach used by most dieters.

RESULTS

Subjects on the low-carbohydrate diet had lost more weight than subjects on the conventional diet at 3 months (mean [±SD], –6.8±5.0 vs. –2.7±3.7 percent of body weight; P=0.001) and 6 months (–7.0±6.5 vs. –3.2±5.6 percent of body weight, P=0.02), but the difference at 12 months was not significant (–4.4±6.7 vs. –2.5±6.3 percent of body weight, P=0.26). After three months, no significant differences were found between the groups in total or low-density lipoprotein cholesterol concentrations. The increase in high-density lipoprotein cholesterol concentrations and the decrease in triglyceride concentrations were greater among subjects on the low-carbohydrate diet than among those on the conventional diet throughout most of the study. Both diets significantly decreased diastolic blood pressure and the insulin response to an oral glucose load.

CONCLUSIONS

The low-carbohydrate diet produced a greater weight loss (absolute difference, approximately 4 percent) than did the conventional diet for the first six months, but the differences were not significant at one year. The low-carbohydrate diet was associated with a greater improvement in some risk factors for coronary heart disease. Adherence was poor and attrition was high in both groups. Longer and larger studies are required to determine the long-term safety and efficacy of low-carbohydrate, high-protein, high-fat diets.

Systematic review of randomized controlled trials of low-carbohydrate vs. low-fat/low-calorie diets in the management of obesity and its comorbidities.

1) M. Hession[1],
2) C. Rolland[1,*],
3) U. Kulkarni[1],
4) A. Wise[2] and
5) J. Broom[1]

Article first published online: 12 AUG 2008

Obesity Reviews
Volume 10, Issue 1, pages 36–50, January 2009

• Summary

There are few studies comparing the effects of low-carbohydrate/high-protein diets with low-fat/high-carbohydrate diets for obesity and cardiovascular disease risk. This systematic review focuses on randomized controlled trials of low-carbohydrate diets compared with low-fat/low-calorie diets. Studies conducted in adult populations with mean or median body mass index of ≥28 kg m^{-2} were included. Thirteen electronic databases were searched and randomized controlled trials from January 2000 to March 2007 were evaluated. Trials were included if they lasted at least 6 months and assessed the weight-loss effects of low-carbohydrate diets against low-fat/low-calorie diets. For each study, data were abstracted and checked by two researchers prior to electronic data entry. The computer program Review Manager 4.2.2 was used for the data analysis. Thirteen articles met the inclusion criteria. There were significant differences between the groups for weight, high-density lipoprotein cholesterol, triacylglycerols and systolic blood pressure, favouring the low-carbohydrate diet. There was a higher attrition rate in the low-fat compared with the low-carbohydrate groups suggesting a patient preference for a low-carbohydrate/high-protein approach as opposed to the Public Health preference of a low-fat/high-carbohydrate diet. Evidence from this systematic review demonstrates that low-carbohydrate/high-protein diets are more effective at 6 months and are as effective, if not more, as low-fat diets in reducing weight and cardiovascular disease risk up to 1 year. More evidence and longer-term studies are needed to assess the long-term cardiovascular benefits from the weight loss achieved using these diets.

Surgical Endoscopy

August 2007, Volume 21, Issue 8, pp 1423-1427

First online: 01 March 2007

The effect of a low-carbohydrate diet on the nonalcoholic fatty liver in morbidly obese patients before bariatric surgery

- O. Benjaminov
- , N. Beglaibter
- , L. Gindy
- , H. Spivak
- , P. Singer
- , M. Wienberg
- , A. Stark
- , M. Rubin

Abstract

Background

Bariatric surgery may be complicated by enlargement of the liver, especially of the left lobe, caused by nonalcoholic fatty liver disease often present with morbid obesity.

Methods

The effect of a very low carbohydrate diet for 4 weeks before surgery on liver density and volume was assessed in 14 candidates for bariatric surgery. Computed tomography (CT) scans were performed before and at termination of the diet period.

Results

The CT scans clearly showed a significant increase in mean liver density ($p = 0.06$) and a decrease in mean liver volume ($p = 0.01$). The increased mean density of the left lobe was markedly greater than that of the right lobe.

Conclusions

The findings show that 4 weeks of a very low carbohydrate diet reduces liver fat content and liver size, particularly of the left lobe. This approach may render bariatric surgery or any foregut operations less difficult in morbidly obese patients and may be a useful treatment for nonalcoholic fatty liver disease.

Nutrition

Volume 31, Issue 1, January 2015, Pages 1–13

Critical review

Dietary carbohydrate restriction as the first approach in diabetes management: Critical review and evidence base

- Richard D. Feinman, Ph.D.[a,*], Wendy K. Pogozelski, Ph.D.[b], Arne Astrup, M.D.[c], Richard K. Bernstein, M.D.[d],
- Eugene J. Fine, M.S., M.D.[e], Eric C. Westman, M.D., M.H.S.[f], Anthony Accurso,M.D.[g], Lynda Frassetto, M.D.[h],
- Barbara A. Gower, Ph.D.[i], Samy I. McFarlane, M.D.[j], Jörgen Vesti Nielsen, M.D.[k], Thure Krarup, M.D.[l]Annika Dahlqvist[r]
- Laura Saslow, Ph.D.[m], Karl S. Roth, M.D.[n], Mary C. Vernon, M.D.[o],Jeff S. Volek, R.D., Ph.D.[p], Gilbert B. Wilshire, M.D.[q],

Highlihgts We present major evidence for low-carbohydrate diets as first approach for diabetes.

Such diets reliably reduce high blood glucose, the most salient feature of diabetes.

Benefits do not require weight loss although nothing is better for weight reduction.

Carbohydrate-restricted diets reduce or eliminate need for medication.

There are no side effects comparable with those seen in intensive pharmacologic treatment.

Abstract

The inability of current recommendations to control the epidemic of diabetes, the specific failure of the prevailing low-fat diets to improve obesity, cardiovascular risk, or general health and the persistent reports of some serious side effects of commonly prescribed diabetic medications, in combination with the continued success of low-carbohydrate diets in the treatment of diabetes and metabolic syndrome without significant side effects, point to the need for a reappraisal of dietary guidelines. The benefits of carbohydrate restriction in diabetes are immediate and well documented. Concerns about the efficacy and safety are long term and conjectural rather than data driven. Dietary carbohydrate restriction reliably reduces high blood glucose, does not require weight loss (although is still best for weight loss), and leads to the reduction or elimination of medication. It has never shown side effects comparable with those seen

in many drugs. Here we present 12 points of evidence supporting the use of low-carbohydrate diets as the first approach to treating type 2 diabetes and as the most effective adjunct to pharmacology in type 1. They represent the best-documented, least controversial results. The insistence on long-term randomized controlled trials as the only kind of data that will be accepted is without precedent in science. The seriousness of diabetes requires that we evaluate all of the evidence that is available. The 12 points are sufficiently compelling that we feel that the burden of proof rests with those who are opposed.

British Journal of Nutrition

- British Journal of Nutrition / Volume 110 / Issue 07 / October 2013, pp 1178–1187

Systematic review with meta-analysis

Very-low-carbohydrate ketogenic diet *v.* low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials

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Abstract

The role of very-low-carbohydrate ketogenic diets (VLCKD) in the long-term management of obesity is not well established. The present meta-analysis aimed to investigate whether individuals assigned to a VLCKD (i.e. a diet with no more than 50 g carbohydrates/d) achieve better long-term body weight and cardiovascular risk factor management when compared with individuals assigned to a conventional low-fat diet (LFD; i.e. a restricted-energy diet with less than 30 % of energy from fat). Through August 2012, MEDLINE, CENTRAL, ScienceDirect, Scopus, LILACS, SciELO, ClinicalTrials.gov and grey literature databases were searched, using no date or language restrictions, for randomised controlled trials that assigned adults to a VLCKD or a LFD, with 12 months or more of follow-up. The primary outcome was body weight. The secondary outcomes were TAG, HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), systolic and diastolic blood pressure, glucose, insulin, HbA_{1c} and C-reactive protein levels. A total of thirteen studies met the inclusion/exclusion criteria. In the overall analysis, five outcomes revealed significant results. Individuals assigned to a VLCKD showed decreased body weight (weighted mean difference − 0·91 (95 % CI − 1·65, − 0·17) kg, 1415 patients), TAG (weighted mean difference − 0·18 (95 % CI − 0·27, − 0·08) mmol/l, 1258 patients) and diastolic blood pressure (weighted mean difference − 1·43 (95 % CI − 2·49, − 0·37) mmHg, 1298 patients) while increased HDL-C (weighted mean difference 0·09 (95 % CI 0·06, 0·12) mmol/l, 1257 patients) and LDL-C (weighted mean difference 0·12 (95 % CI 0·04, 0·2) mmol/l, 1255 patients). Individuals assigned to a VLCKD achieve a greater weight loss than those assigned to a LFD in the long term; hence, a VLCKD may be an alternative tool against obesity.

2015 American Society for Nutrition

A Lower-Carbohydrate, Higher-Fat Diet Reduces Abdominal and Intermuscular Fat and Increases Insulin Sensitivity in Adults at Risk of Type 2 Diabetes[1,2,3]

1. **Barbara A Gower*** **and**
2. **Amy M Goss**

+Author Affiliations

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1. ↵* To whom correspondence should be addressed. E-mail: bgower@uab.edu.

Abstract

Background:

Obesity, particularly visceral and ectopic adiposity, increases the risk of type 2 diabetes.

Objective:

The aim of this study was to determine if restriction of dietary carbohydrate is beneficial for body composition and metabolic health.

Methods:

Two studies were conducted. In the first, 69 overweight/obese men and women, 53% of whom were European American (EA) and 47% of whom were African American (AA), were provided with 1 of 2 diets (lower-fat diet: 55%, 18%, and 27% of energy from carbohydrate, protein, and fat, respectively; lower-carbohydrate diet: 43%, 18%, and 39%, respectively) for 8 wk at a eucaloric level and 8 wk at a hypocaloric level. In the second study, 30 women with polycystic ovary syndrome (PCOS) were provided with 2 diets (lower-fat diet: 55%, 18%, and 27% of energy from carbohydrate, protein, and fat, respectively; lower-carbohydrate diet: 41%, 19%, and 40%, respectively) at a eucaloric level for 8 wk in a random-order crossover design.

Results:

As previously reported, among overweight/obese adults, after the eucaloric phase, participants who consumed the lower-carbohydrate vs. the lower-fat diet lost more intra-abdominal adipose tissue (IAAT) (11 ± 3% vs. 1 ± 3%; $P < 0.05$). After weight loss, participants who consumed the lower-carbohydrate diet had 4.4% less total fat mass. Original to this report, across the entire 16-wk study, AAs lost more fat mass with a lower-carbohydrate diet (6.2 vs. 2.9 kg; $P < 0.01$), whereas EAs showed no difference between diets. As previously reported, among women with PCOS, the lower-carbohydrate arm showed decreased fasting insulin (−2.8 μIU/mL; $P < 0.001$) and fasting glucose (−4.7 mg/dL; $P < 0.01$) and increased insulin sensitivity (1.06 arbitrary units; $P < 0.05$) and "dynamic" β-cell response ($96.1 \cdot 10^9$; $P < 0.001$). In the

lower-carbohydrate arm, women lost both IAAT (−4.8 cm^2; $P < 0.01$) and intermuscular fat (−1.2 cm^2; $P < 0.01$). In the lower-fat arm, women lost lean mass (−0.6 kg; $P < 0.05$). Original to this report, after the lower-carbohydrate arm, the change in IAAT was positively associated with the change in tumor necrosis factor α ($P < 0.05$).

Conclusion:
A modest reduction in dietary carbohydrate has beneficial effects on body composition, fat distribution, and glucose metabolism. This trial was registered at clinicaltrials.gov as NCT00726908 and NCT01028989.

Exp Clin Cardiol. 2004 Fall; 9(3): 200–205. Clinical Cardiology

Long-term effects of a ketogenic diet in obese patients

Hussein M Dashti, MD PhD FICS FACS,[1] Thazhumpal C Mathew, MSc PhD FRCPath,[4] Talib Hussein, MB ChB,[5] Sami K Asfar, MB ChB MD FRCSEd FACS,[1] Abdulla Behbahani, MB ChB FRCS FACSI PhD FICS FACS,[1] Mousa A Khoursheed, MB ChB FRCS FICS,[1] Hilal M Al-Sayer, MD PhD FICS FACS,[1] Yousef Y Bo-Abbas, MD FRCPC,[2] and Naji S Al-Zaid, BSc PhD[3]

Abstract

BACKGROUND:
Although various studies have examined the short-term effects of a ketogenic diet in reducing weight in obese patients, its long-term effects on various physical and biochemical parameters are not known.

OBJECTIVE:
To determine the effects of a 24-week ketogenic diet (consisting of 30 g carbohydrate, 1 g/kg body weight protein, 20% saturated fat, and 80% polyunsaturated and monounsaturated fat) in obese patients.

PATIENTS AND METHODS:
In the present study, 83 obese patients (39 men and 44 women) with a body mass index greater than 35 kg/m^2, and high glucose and cholesterol levels were selected. The body weight, body mass index, total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, fasting blood sugar, urea and creatinine levels were determined before and after the administration of the ketogenic diet. Changes in these parameters were monitored after eight, 16 and 24 weeks of treatment.

RESULTS:
The weight and body mass index of the patients decreased significantly ($P<0.0001$). The level of total cholesterol decreased from week 1 to week 24. HDL cholesterol levels significantly increased, whereas LDL cholesterol levels significantly decreased after treatment. The level of triglycerides decreased significantly following 24 weeks of treatment. The level of blood glucose significantly decreased. The changes in the level of urea and creatinine were not statistically significant.

CONCLUSIONS:
The present study shows the beneficial effects of a long-term ketogenic diet. It significantly reduced the body weight and body mass index of the patients. Furthermore, it decreased the level of triglycerides, LDL cholesterol and blood glucose, and increased the level of HDL

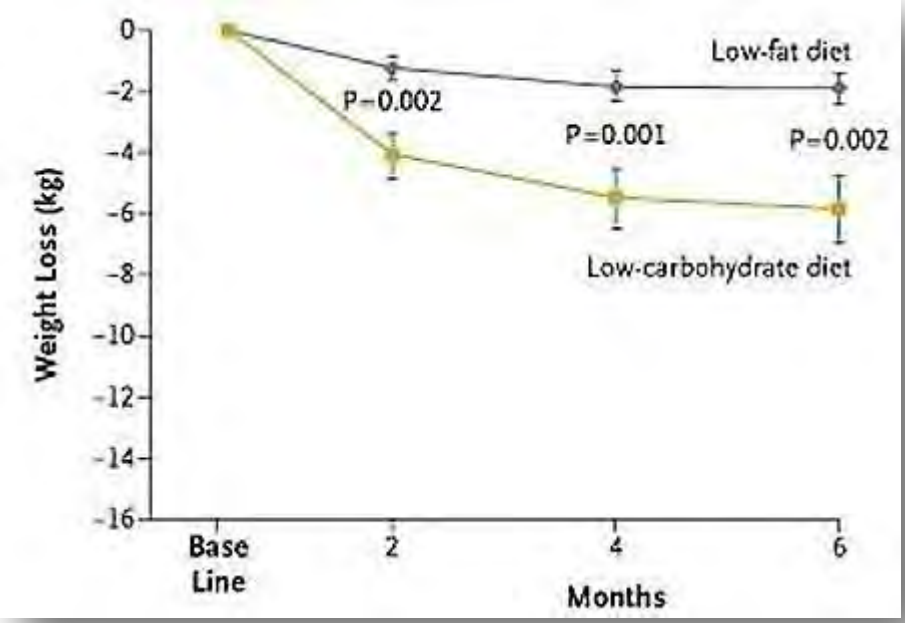
cholesterol. Administering a ketogenic diet for a relatively longer period of time did not produce any significant side effects in the patients. Therefore, the present study confirms that it is safe to use a ketogenic diet for a longer period of time than previously demonstrated.

A low-carbohydrate as compared with a low-fat diet in severe obesity.

Samaha FF, et al. New England Journal of Medicine, 2003.

Details: 132 individuals with severe obesity (mean BMI of 43) were randomized to either a low-fat or a low-carb diet. Many of the subjects had metabolic syndrome or type II diabetes. The low-fat dieters were calorie restricted. Study duration was 6 months.

Weight Loss: The low-carb group lost an average of 5.8 kg (12.8 lbs) while the low-fat group lost only 1.9 kg (4.2 lbs). The difference was statistically significant.



Conclusion: The low-carb group lost significantly more weight (about 3 times as much). There was also a statistically significant difference in several biomarkers:

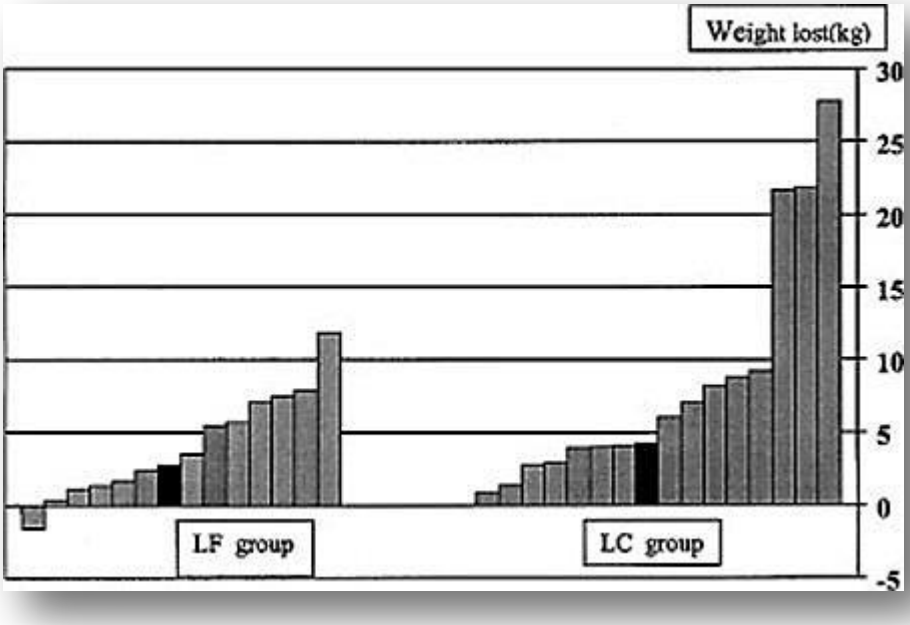
- **Triglycerides** went down by 38 mg/dL in the LC group, compared to 7 mg/dL in the LF group.
- **Insulin sensitivity** improved on LC, got slightly worse on LF.
- **Fasting blood glucose** levels went down by 26 mg/dL in the LC group, only 5 mg/dL in the LF group.
- **Insulin** levels went down by 27% in the LC group, but increased slightly in the LF group. Overall, the low-carb diet had significantly more beneficial effects on weight and key biomarkers in this group of severely obese individuals.

Effects of a low-carbohydrate diet on weight loss and cardiovascular risk factor in overweight adolescents.

Sondike SB, et al. The Journal of Pediatrics, 2003.

Details: 30 overweight adolescents were randomized to two groups, a low-carb diet group and a low-fat diet group. This study went on for 12 weeks. Neither group was instructed to restrict calories.

Weight Loss: The low-carb group lost 9.9 kg (21.8 lbs), while the low-fat group lost 4.1 kg (9 lbs). The difference was statistically significant.



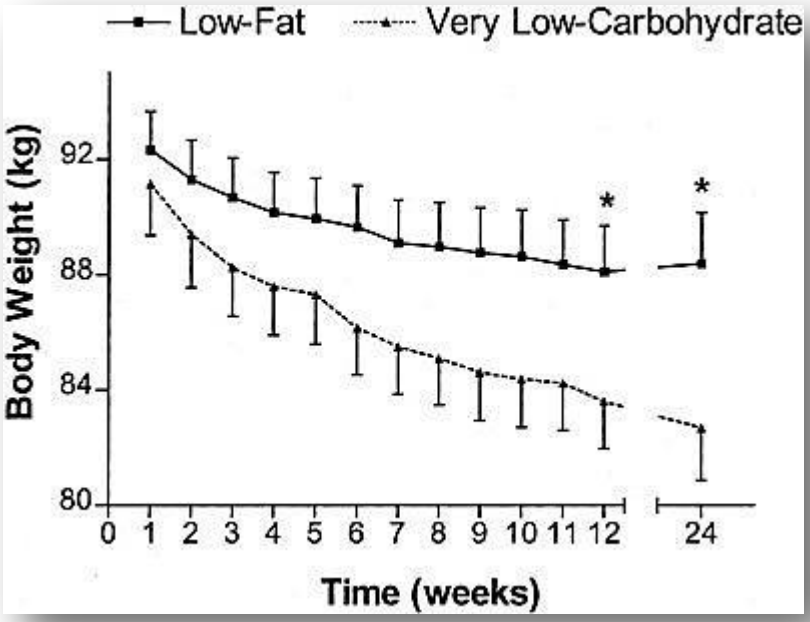
Conclusion: The low-carb group lost significantly more (2.3 times as much) weight and had significant decreases in Triglycerides and Non-HDL cholesterol. Total and LDL cholesterol decreased in the low-fat group only.

A randomized trial comparing a very low carbohydrate diet and a calorie-restricted low fat diet on body weight and cardiovascular risk factors in healthy women.

Brehm BJ, et al. The Journal of Clinical Endocrinology & Metabolism, 2003.

Details: 53 healthy but obese females were randomized to either a low-fat diet, or a low-carb diet. Low-fat group was calorie restricted. The study went on for 6 months.

Weight Loss: The women in the low-carb group lost an average og 8.5 kg (18.7 lbs), while the low-fat group lost an average of 3.9 kg (8.6 lbs). The difference was statistically significant at 6 months.



Conclusion: The low-carb group lost more weight (2.2 times as much) and had significant reductions in blood triglycerides. HDL improved slightly in both groups.

The national cholesterol education program diet vs a diet lower in carbohydrates and higher in protein and monounsaturated fat.

5. Aude YW, et al. Archives of Internal Medicine, 2004.

Details: 60 overweight individuals were randomized to a low-carb diet high in monounsaturated fat, or a low-fat diet based on the National Cholesterol Education Program (NCEP).

Both groups were calorie restricted and the study went on for 12 weeks.

Weight Loss: The low-carb group lost an average of 6.2 kg (13.6 lbs), while the low-fat group lost 3.4 kg (7.5 lbs). The difference was statistically significant.

Conclusion: The low-carb group lost 1.8 times as much weight. There were also several changes in biomarkers that are worth noting:

- **Waist-to-hip ratio** is a marker for abdominal fat. This marker improved slightly in the LC group, not in the LF group.
- **Total cholesterol** improved in both groups.
- **Triglycerides** went down by 42 mg/dL in the LC group, compared to 15.3 mg/dL in the LF group.
- **LDL particle size** increased by 4.8 nm and percentage of **small, dense LDL**decreased by 6.1% in the LC group, while there was no significant difference in the LF group.

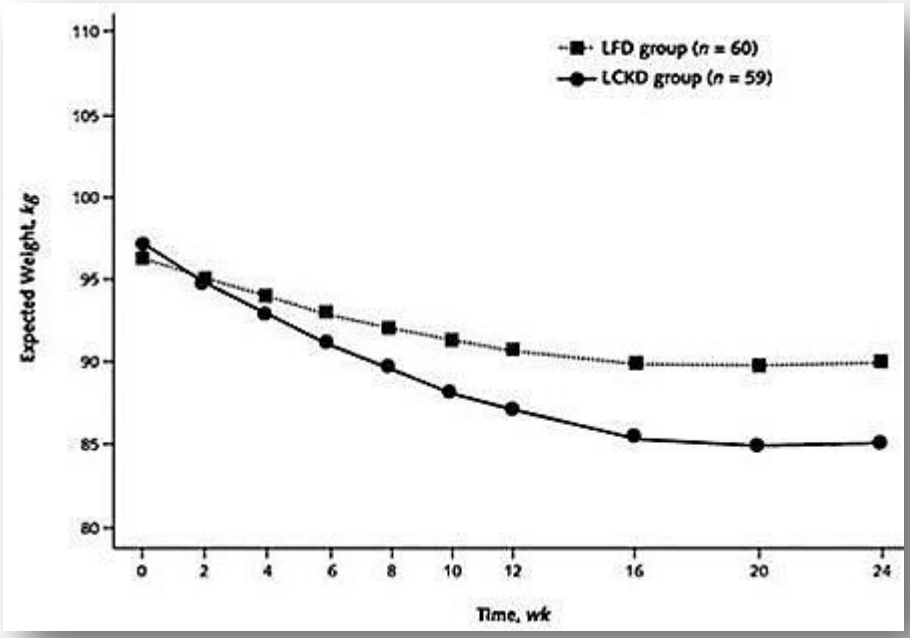
Overall, the low-carb group lost more weight and had much greater improvements in several important risk factors for cardiovascular disease.

A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia.

Yancy WS Jr, et al. Annals of Internal Medicine, 2004.

Details: 120 overweight individuals with elevated blood lipids were randomized to a low-carb or a low-fat diet. The low-fat group was calorie restricted. Study went on for 24 weeks.

Weight Loss: The low-carb group lost 9.4 kg (20.7 lbs) of their total body weight, compared to 4.8 kg (10.6 lbs) in the low-fat group.



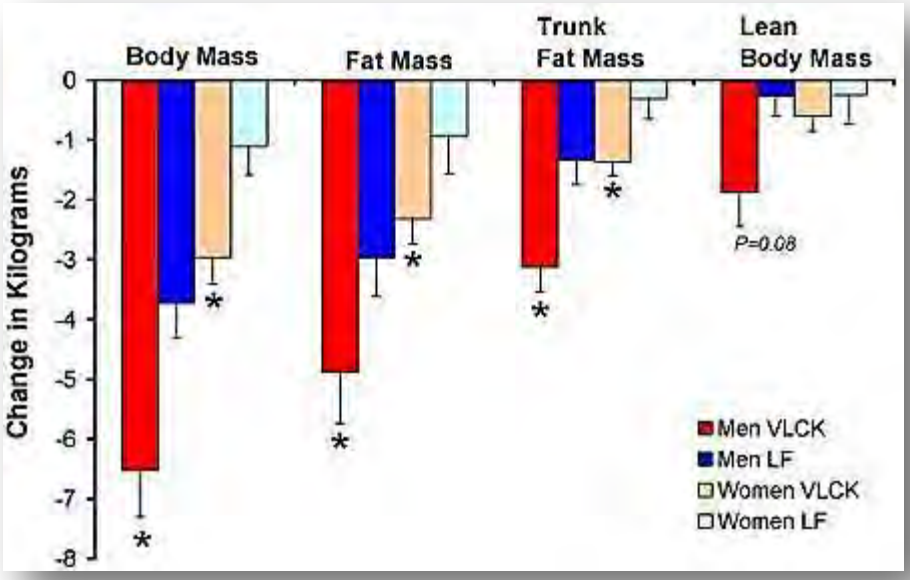
Conclusion: The low-carb group lost significantly more weight and had greater improvements in blood triglycerides and HDL cholesterol.

Comparison of energy-restricted very low-carbohydrate and low-fat diets on weight loss and body composition in overweight men and women.

JS Volek, et al. Nutrition & Metabolism (London), 2004.

Details: A randomized, crossover trial with 28 overweight/obese individuals. Study went on for 30 days (for women) and 50 days (for men) on each diet, that is a very low-carb diet and a low-fat diet. Both diets were calorie restricted.

Weight Loss: The low-carb group lost significantly more weight, especially the men. This was despite the fact that they ended up eating more calories than the low-fat group.



Conclusion: The low-carb group lost more weight. The men on the low-carb diet lost three times as much abdominal fat as the men on the low-fat diet.

Comparison of a low-fat diet to a low-carbohydrate diet on weight loss, body composition, and risk factors for diabetes and cardiovascular disease in free-living, overweight men and women.

Meckling KA, et al. The Journal of Clinical Endocrinology & Metabolism, 2004.

Details: 40 overweight individuals were randomized to a low-carb and a low-fat diet for 10 weeks. The calories were matched between groups.

Weight Loss: The low-carb group lost 7.0 kg (15.4 lbs) and the low-fat group lost 6.8 kg (14.9 lbs). The difference was not statistically significant.

Conclusion: Both groups lost a similar amount of weight.

A few other notable differences in biomarkers:

- **Blood pressure** decreased in both groups, both systolic and diastolic.
- **Total and LDL cholesterol** decreased in the LF group only.
- **Triglycerides** decreased in both groups.
- **HDL cholesterol** went up in the LC group, but decreased in the LF group.
- **Blood sugar** went down in both groups, but only the LC group had decreases in**insulin** levels, indicating improved insulin sensitivity.

Perceived hunger is lower and weight loss is greater in overweight premenopausal women consuming a low-carbohydrate/high-protein vs high-carbohydrate/low-fat diet.

Nickols-Richardson SM, et al. Journal of the American Dietetic Association, 2005.

Details: 28 overweight premenopausal women consumed either a low-carb or a low-fat diet for 6 weeks. The low-fat group was calorie restricted.

Weight Loss: The women in the low-carb group lost 6.4 kg (14.1 lbs) compared to the low-fat group, which lost 4.2 kg (9.3 lbs). The results were statistically significant.

Conclusion: The low-carb diet caused significantly more weight loss and reduced hunger compared to the low-fat diet.

The effects of a low-carbohydrate ketogenic diet and a low-fat diet on mood, hunger, and other self-reported symptoms.

McClernon FJ, et al. Obesity (Silver Spring), 2007.

Details: 119 overweight individuals were randomized to a low-carb, ketogenic diet or a calorie restricted low-fat diet for 6 months.

Weight Loss: The low-carb group lost 12.9 kg (28.4 lbs), while the low-fat group lost only 6.7 kg (14.7 lbs).

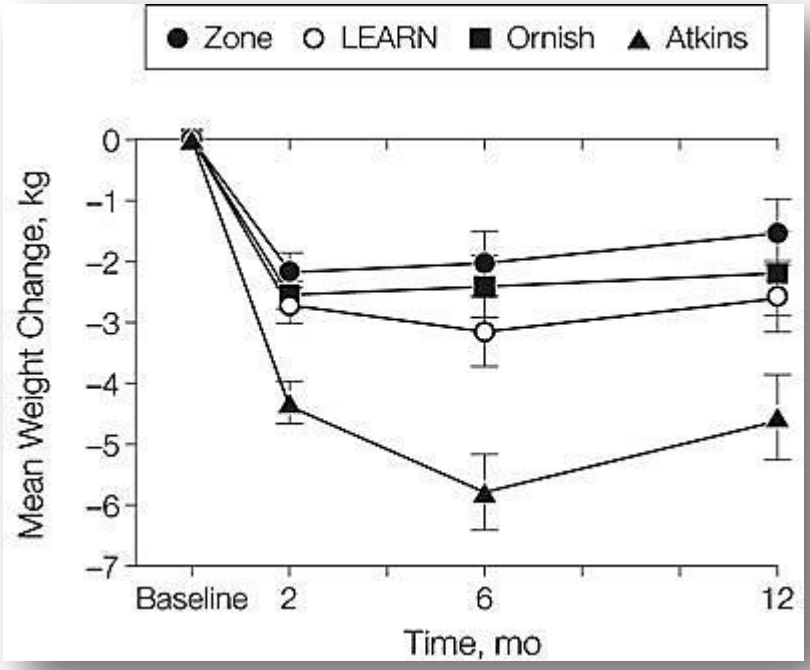
Conclusion: The low-carb group lost almost twice the weight and experienced less hunger.

Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: the A TO Z Weight Loss Study.

Gardner CD, et al.The Journal of The American Medical Association, 2007.

Details: 311 overweight/obese premenopausal women were randomized to 4 diets: A low-carb Atkins diet, a low-fat vegetarian Ornish diet, the Zone diet and the LEARN diet. Zone and LEARN were calorie restricted.

Weight Loss: The Atkins group lost the most weight at 12 months (4.7 kg – 10.3 lbs) compared to Ornish (2.2 kg – 4.9 lbs), Zone (1.6 kg – 3.5 lbs) and LEARN (2.6 kg – 5.7 lbs). However, the difference was not statistically significant at 12 months.



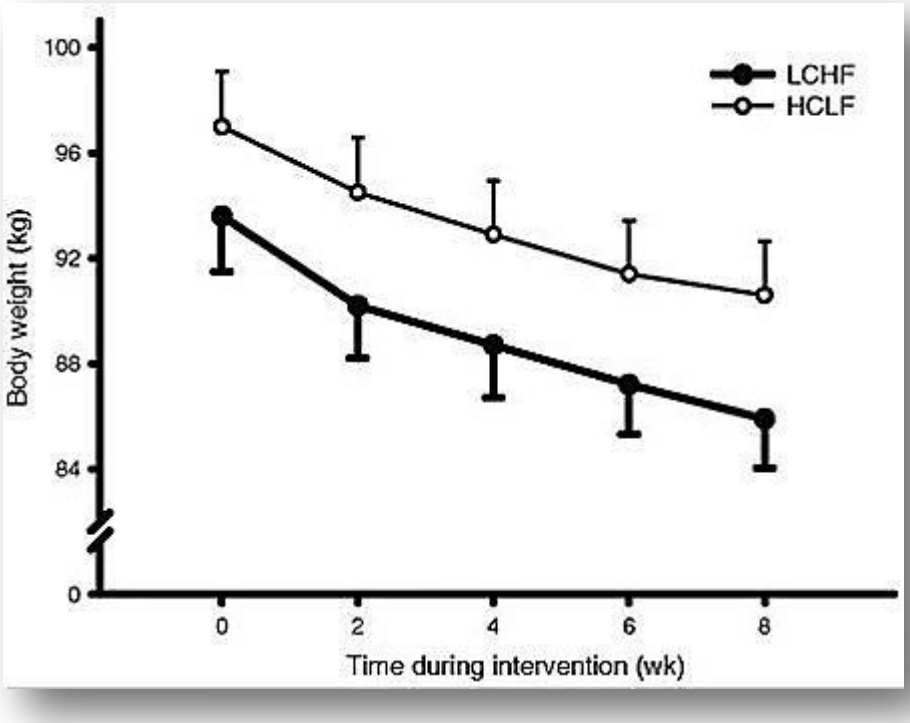
Conclusion: The Atkins group lost the most weight, although the difference was not statistically significant. The Atkins group had the greatest improvements in blood pressure, triglycerides and HDL. LEARN and Ornish (low-fat) had decreases in LDL at 2 months, but then the effects diminished.

Low- and high-carbohydrate weight-loss diets have similar effects on mood but not cognitive performance.

Halyburton AK, et al. American Journal of Clinical Nutrition, 2007.

Details: 93 overweight/obese individuals were randomized to either a low-carb, high-fat diet or a low-fat, high-carb diet for 8 weeks. Both groups were calorie restricted.

Weight Loss: The low-carb group lost 7.8 kg (17.2 lbs), while the low-fat group lost 6.4 kg (14.1 lbs). The difference was statistically significant.



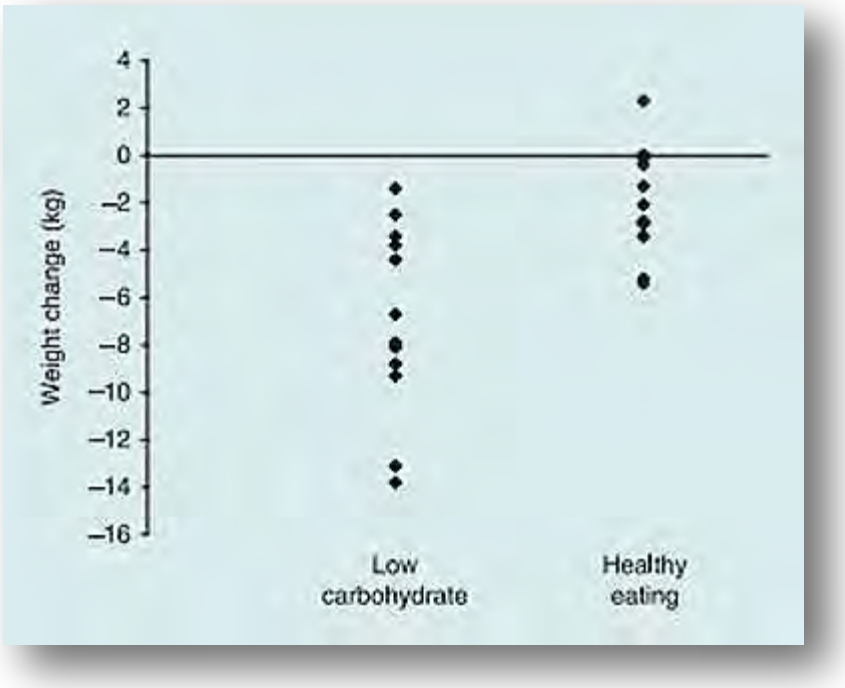
Conclusion: The low-carb group lost more weight. Both groups had similar improvements in mood, but speed of processing (a measure of cognitive performance) improved further on the low-fat diet.

A low-carbohydrate diet is more effective in reducing body weight than healthy eating in both diabetic and non-diabetic subjects.

Dyson PA, et al. Diabetic Medicine, 2007.

Details: 13 diabetic and 13 non-diabetic individuals were randomized to a low-carb diet or a "healthy eating" diet that followed the Diabetes UK recommendations (a calorie restricted, low-fat diet). Study went on for 3 months.

Weight Loss: The low-carb group lost 6.9 kg (15.2 lbs), compared to 2.1 kg (4.6 lbs) in the low-fat group.



Conclusion: The low-carb group lost more weight (about 3 times as much). There was no difference in any other marker between groups.

The effect of a low-carbohydrate, ketogenic diet versus a low-glycemic index diet on glycemic control in type 2 diabetes mellitus.

Westman EC, et al. Nutrion & Metabolism (London), 2008.

Details: 84 individuals with obesity and type 2 diabetes were randomized to a low-carb, ketogenic diet or a calorie restricted low-glycemic diet. The study went on for 24 weeks.

Weight Loss: The low-carb group lost more weight (11.1 kg – 24.4 lbs) compared to the low-glycemic group (6.9 kg – 15.2 lbs).

Conclusion: The low-carb group lost significantly more weight than the low-glycemic group. There were several other important differences:

- **Hemoglobin A1c** went down by 1.5% in the LC group, compared to 0.5% in the low-glycemic group.
- **HDL cholesterol** increased in the LC group only, by 5.6 mg/dL.
- **Diabetes medications** were either reduced or eliminated in 95.2% of the LC group, compared to 62% in the low-glycemic group.
- Many other health markers like blood pressure and triglycerides improved in both groups, but the difference between groups was not statistically significant.

Effects of weight loss from a very-low-carbohydrate diet on endothelial function and markers of cardiovascular disease risk in subjects with abdominal obesity.

Keogh JB, et al.

American Journal of Clinical Nutrition, 2008.

Details: 107 individuals with abdominal obesity were randomized to a low-carb or a low-fat diet. Both groups were calorie restricted and the study went on for 8 weeks.

Weight Loss: The low-carb group lost 7.9% of body weight, compared to the low-fat group which lost 6.5% of body weight.

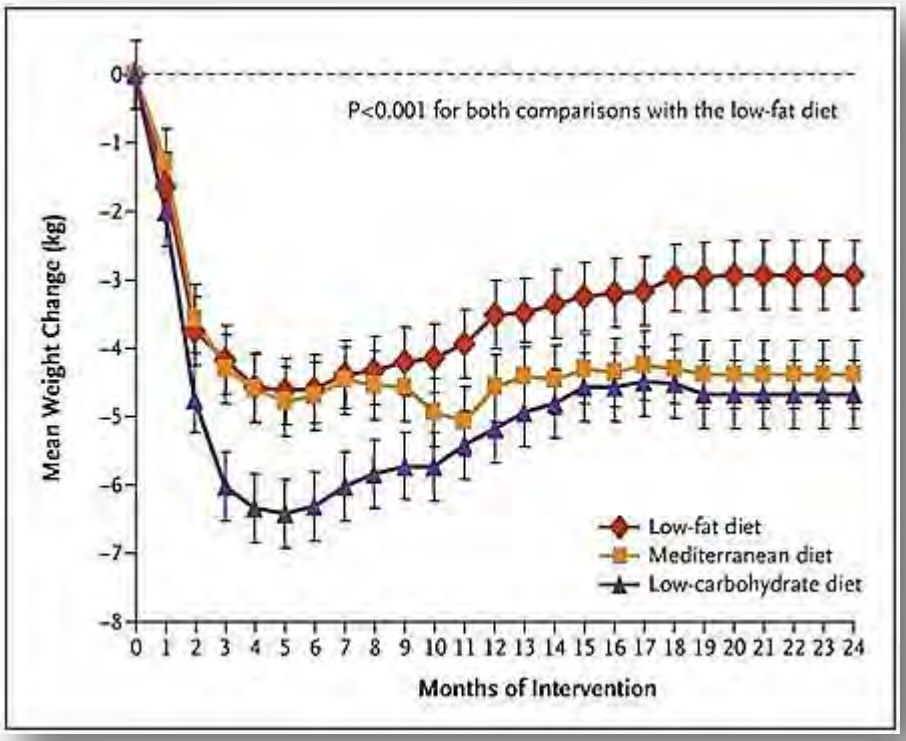
Conclusion: The low-carb group lost more weight and there was no difference between groups on Flow Mediated Dilation or any other markers of the function of the endothelium (the lining of blood vessels). There was also no difference in common risk factors between groups.

Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet.

Shai I, et al. New England Journal of Medicine, 2008.

Details: 322 obese individuals were randomized to three diets: a low-carb diet, a calorie restricted low-fat diet and a calorie restricted Mediterranean diet. Study went on for 2 years.

Weight Loss: The low-carb group lost 4.7 kg (10.4 lbs), the low-fat group lost 2.9 kg (6.4 lbs) and the Mediterranean diet group lost 4.4 kg (9.7 lbs).



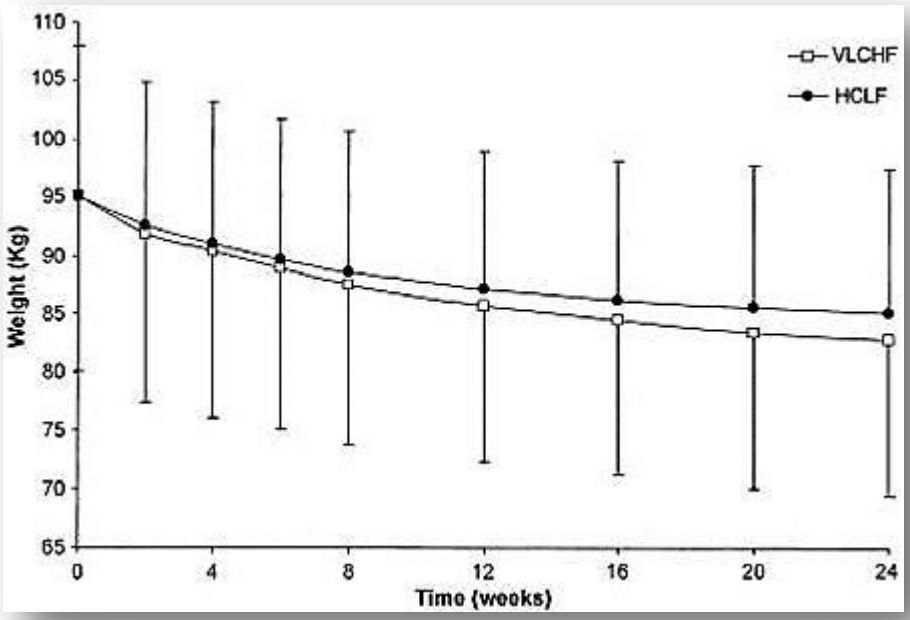
Conclusion: The low-carb group lost more weight than the low-fat group and had greater improvements in HDL cholesterol and triglycerides.

Metabolic effects of weight loss on a very-low-carbohydrate diet compared with an isocaloric high-carbohydrate diet in abdominally obese subjects.

Tay J, et al. Journal of The American College of Cardiology, 2008.

Details: 88 individuals with abdominal obesity were randomized to a very low-carb or a low-fat diet for 24 weeks. Both diets were calorie restricted.

Weight Loss: The low-carb group lost an average of 11.9 kg (26.2 lbs), while the low-fat group lost 10.1 kg (22.3 lbs). However, the difference was not statistically significant.



Conclusion: The low-carb group lost more weight. Triglycerides, HDL, C-Reactive Protein, Insulin, Insulin Sensitivity and Blood Pressure improved in both groups. Total and LDL cholesterol improved in the low-fat group only.

Carbohydrate restriction has a more favorable impact on the metabolic syndrome than a low fat diet.

Volek JS, et al. Lipids, 2009.

Details: 40 subjects with elevated risk factors for cardiovascular disease were randomized to a low-carb or a low-fat diet for 12 weeks. Both groups were calorie restricted.

Weight Loss: The low-carb group lost 10.1 kg (22.3), while the low-fat group lost 5.2 kg (11.5 lbs).

Conclusion: The low-carb group lost almost twice the amount of weight as the low-fat group, despite eating the same amount of calories.

This study is particularly interesting because it matched calories between groups and measured so-called "advanced" lipid markers. Several things are worth noting:

- **Triglycerides** went down by 107 mg/dL on LC, but 36 mg/dL on the LF diet.
- **HDL cholesterol** increased by 4 mg/dL on LC, but went down by 1 mg/dL on LF.
- **Apolipoprotein B** went down by 11 points on LC, but only 2 points on LF.
- **LDL size** increased on LC, but stayed the same on LF.
- On the LC diet, the LDL particles partly shifted from small to large (good), while they partly shifted from large to small on LF (bad).

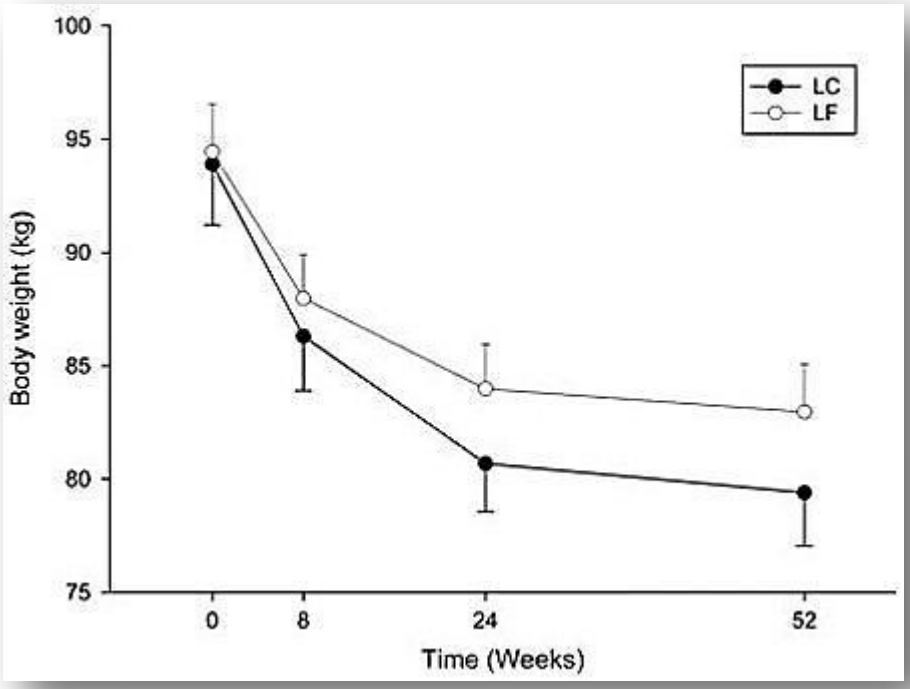
Long-term effects of a very-low-carbohydrate weight loss diet compared with an isocaloric low-fat diet after 12 months.

Brinkworth GD, et al.

American Journal of Clinical Nutrition, 2009.

Details: 118 individuals with abdominal obesity were randomized to a low-carb or a low-fat diet for 1 year. Both diets were calorie restricted.

Weight Loss: The low-carb group lost 14.5 kg (32 lbs), while the low-fat group lost 11.5 kg (25.3 lbs) but the difference was not statistically significant.



Conclusion: The low-carb group had greater decreases in triglycerides and greater increases in both HDL and LDL cholesterol, compared to the low-fat group.

Lack of suppression of circulating free fatty acids and hypercholesterolemia during weight loss on a high-fat, low-carbohydrate diet.

Hernandez, et al.

American Journal of Clinical Nutrition, 2010.

Details: 32 obese adults were randomized to a low-carb or a calorie restricted, low-fat diet for 6 weeks.

Weight Loss: The low-carb group lost 6.2 kg (13.7 lbs) while the low-fat group lost 6.0 kg (13.2 lbs). The difference was not statistically significant.

Conclusion: The low-carb group had greater decreases in triglycerides (43.6 mg/dL) than the low-fat group (26.9 mg/dL). Both LDL and HDL decreased in the low-fat group only.

In type 2 diabetes, randomization to advice to follow a low-carbohydrate diet transiently improves glycaemic control compared with advice to follow a low-fat diet producing a similar weight loss.

Guldbrand, et al. Diabetologia, 2012.

Details: 61 individuals with type 2 diabetes were randomized to a low-carb or a low-fat diet for 2 years. Both diets were calorie restricted.

Weight Loss: The low-carb group lost 3.1 kg (6.8 lbs), while the low-fat group lost 3.6 kg (7.9 lbs). The difference was not statistically significant.

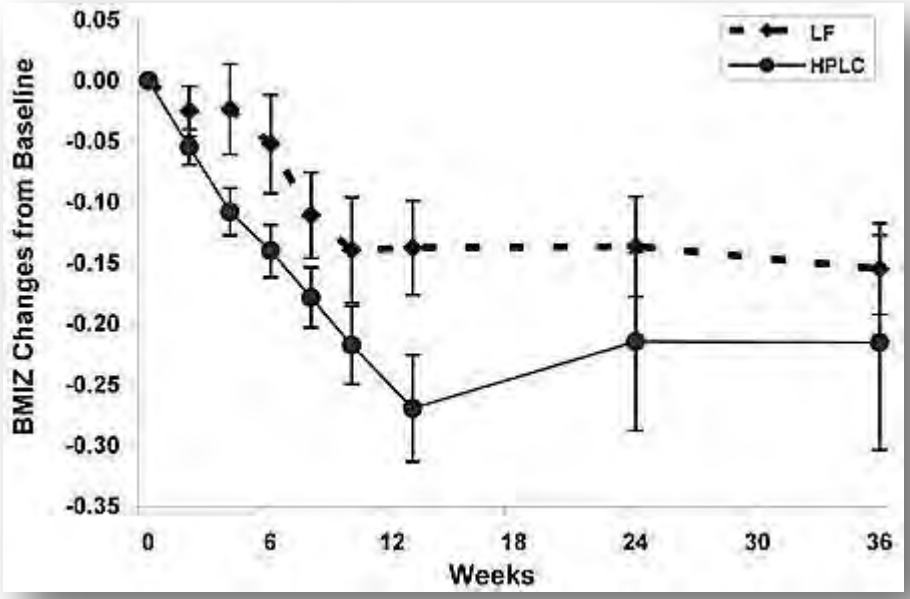
Conclusion: There was no difference in weight loss or common risk factors between groups. There was significant improvement in glycemic control at 6 months for the low-carb group, but compliance was poor and the effects diminished at 24 months as individuals had increased their carb intake

Efficacy and safety of a high protein, low carbohydrate diet for weight loss in severely obese adolescents.

Krebs NF, et al. Journal of Pediatrics, 2010.

Details: 46 individuals were randomized to a low-carb or a low-fat diet for 36 weeks. Low-fat group was calorie restricted.

Weight Loss: The low-carb group lost more weight and had greater decreases in BMI than the low-fat group.

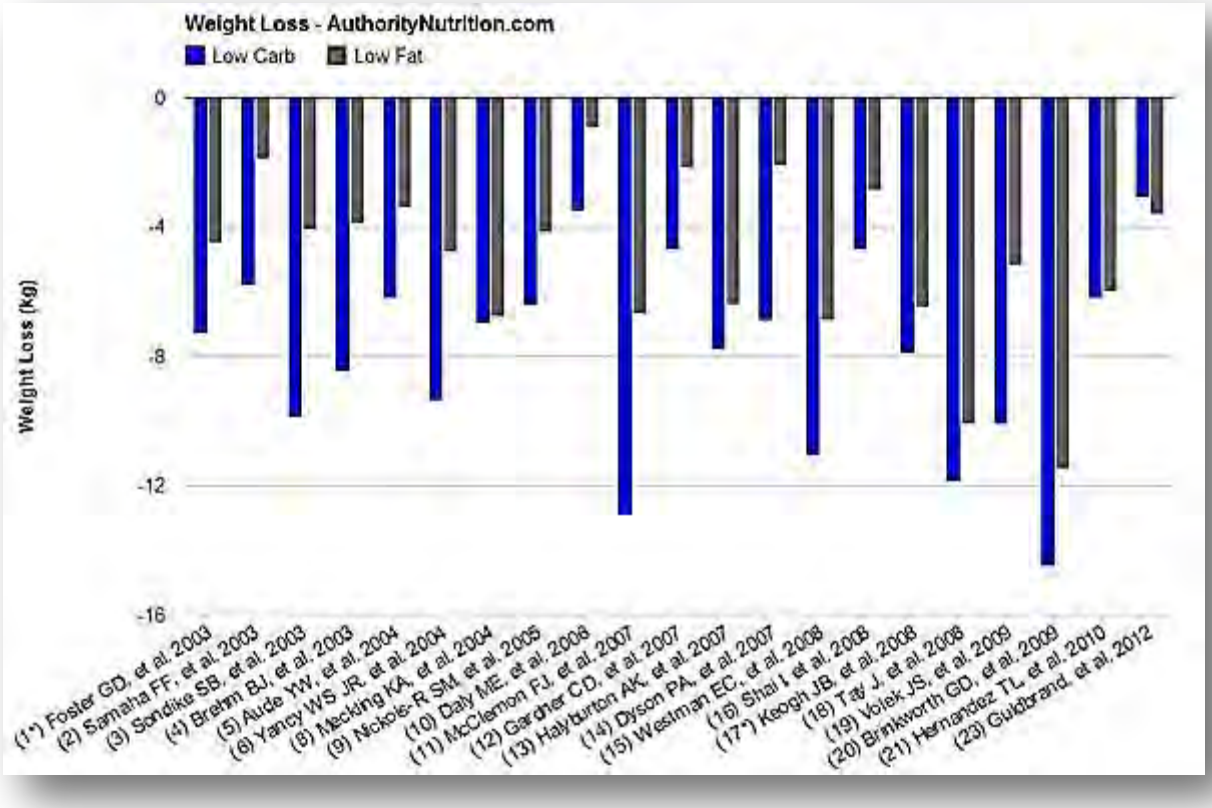


Conclusion: The low-carb group had greater reductions in BMI. Various biomarkers improved in both groups, but there was no significant difference between groups.

Summary of 23 scientific works with low-carbohydrate diet

Weight Loss

Here is a graph that shows the difference in weight loss between studies. 21 of 23 studies reported weight loss numbers:



The majority of studies achieved statistically significant differences in weight loss (always in favor of low-carb). There are several other factors that are worth noting:

- The low-carb groups often lost 2-3 times as much weight as the low-fat groups. In a few instances there was no significant difference.
- In most cases, calories were restricted in the low-fat groups, while the low-carb groups could eat as much as they wanted.
- When both groups restricted calories, the low-carb dieters still lost more weight (7, 13, 19), although it was not always significant (8, 18, 20).

- There was only one study where the low-fat group lost more weight (23) although the difference was small (0.5 kg – 1.1 lb) and not statistically significant.
- In several of the studies, weight loss was greatest in the beginning. Then people start regaining the weight over time as they abandon the diet.
- When the researchers looked at abdominal fat (the unhealthy visceral fat) directly, low-carb diets had a clear advantage (5, 7, 19).

LDL Cholesterol

Despite the concerns expressed by many people, low-carb diets generally do not raise Total and LDL cholesterol levels on average.

Low-fat diets do lower Total and LDL cholesterol, but it is usually only temporary. After 6 to 12 months, the difference is not statistically significant.

There have been some anecdotal reports by doctors who treat patients with low-carb diets, that they can lead to increases in LDL cholesterol and some advanced lipid markers for a small percentage of individuals.

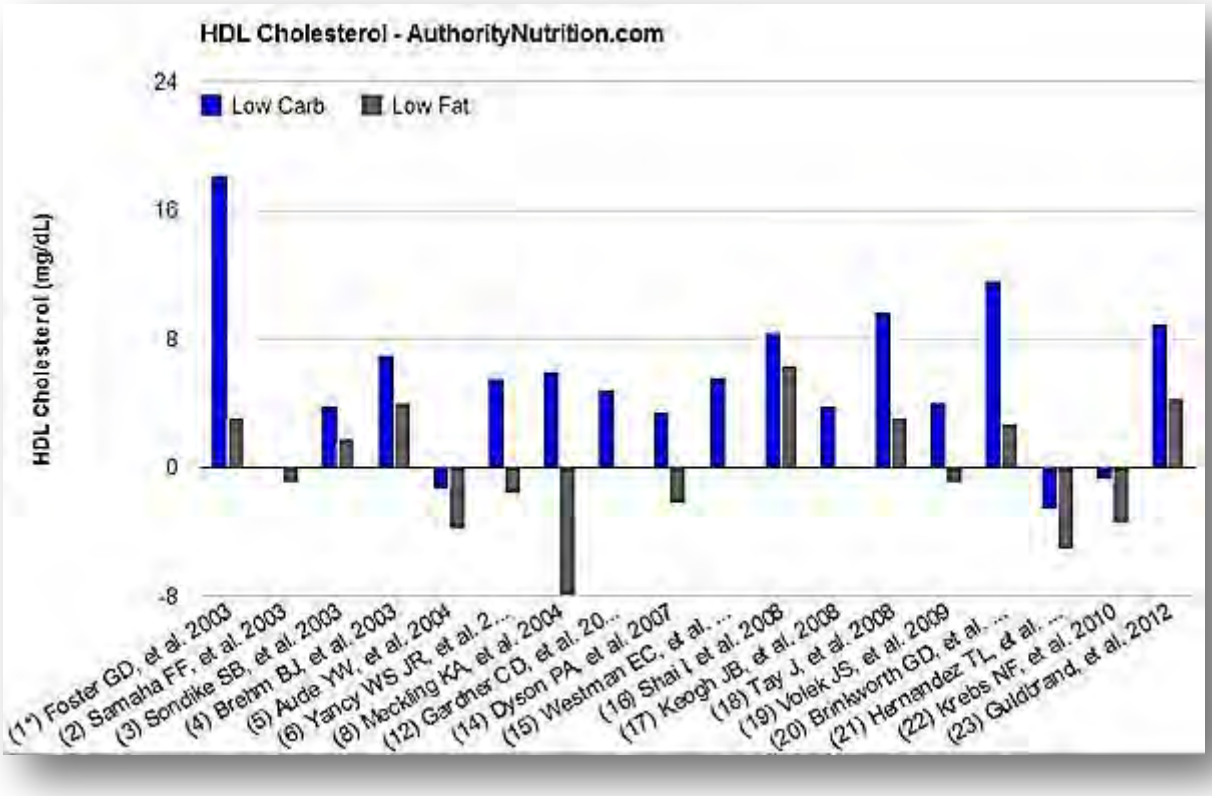
However, none of the studies above noted such adverse effects. The few studies that looked at advanced lipid markers (5, 19) only showed improvements.

HDL Cholesterol

One of the best ways to raise HDL cholesterol levels is to eat more fat. For this reason, it is not surprising to see that low-carb diets (higher in fat) raise HDL significantly more than low-fat diets.

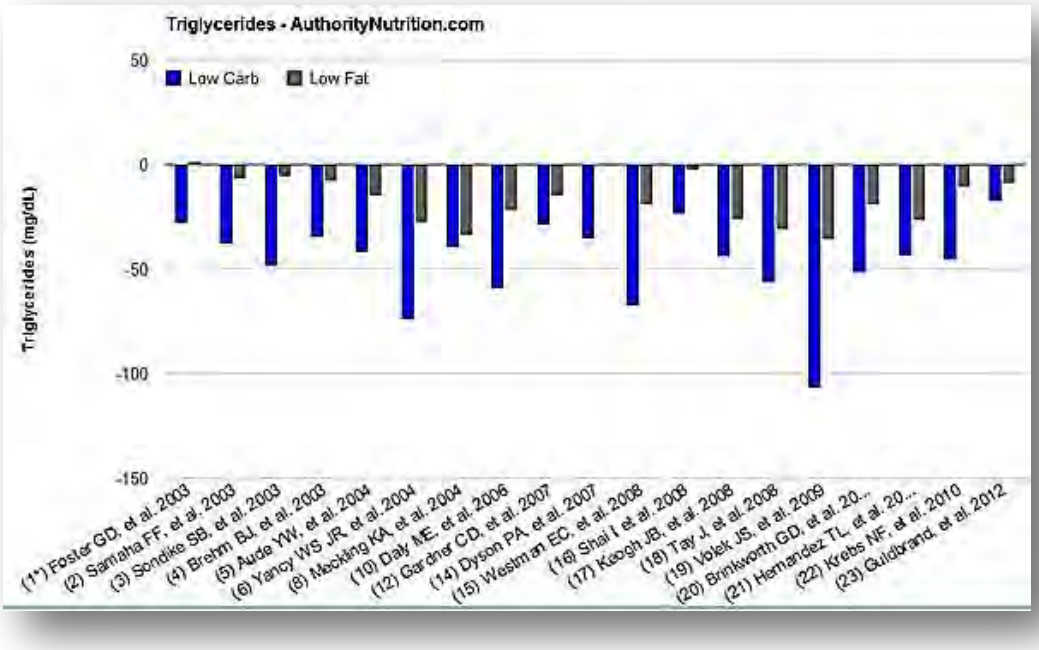
Having higher HDL levels is correlated with improved metabolic health and a lower risk of cardiovascular disease. Having low HDL levels is one of the key symptoms of the metabolic syndrome.

18 of the 23 studies reported changes in HDL cholesterol levels:



You can see that low-carb diets generally raise HDL levels, while they don't change as much on low-fat diets and in some cases go down.

Triglycerides – Triglycerides are an important cardiovascular risk factor and another key symptom of the metabolic syndrome.The best way to reduce triglycerides is to eat less carbohydrates, especially sugar. 19 of 23 studies reported changes in blood triglyceride levels:



It is clear that both low-carb and low-fat diets lead to reductions in triglycerides, but the effect is much stronger in the low-carb groups.

Blood Sugar, Insulin Levels and Type II Diabetes

In non-diabetics, blood sugar and insulin levels improved on both low-carb and low-fat diets and the difference between groups was usually small.

3 studies compared low-carb and low-fat diets in Type 2 diabetic patients.

Only one of those studies had good compliance and managed to reduce carbohydrates sufficiently. This lead various improvements and a drastic reduction in HbA1c, a marker for blood sugar levels (15).

In this study, over 90% of the individuals in the low-carb group managed to reduce or eliminate their diabetes medications.

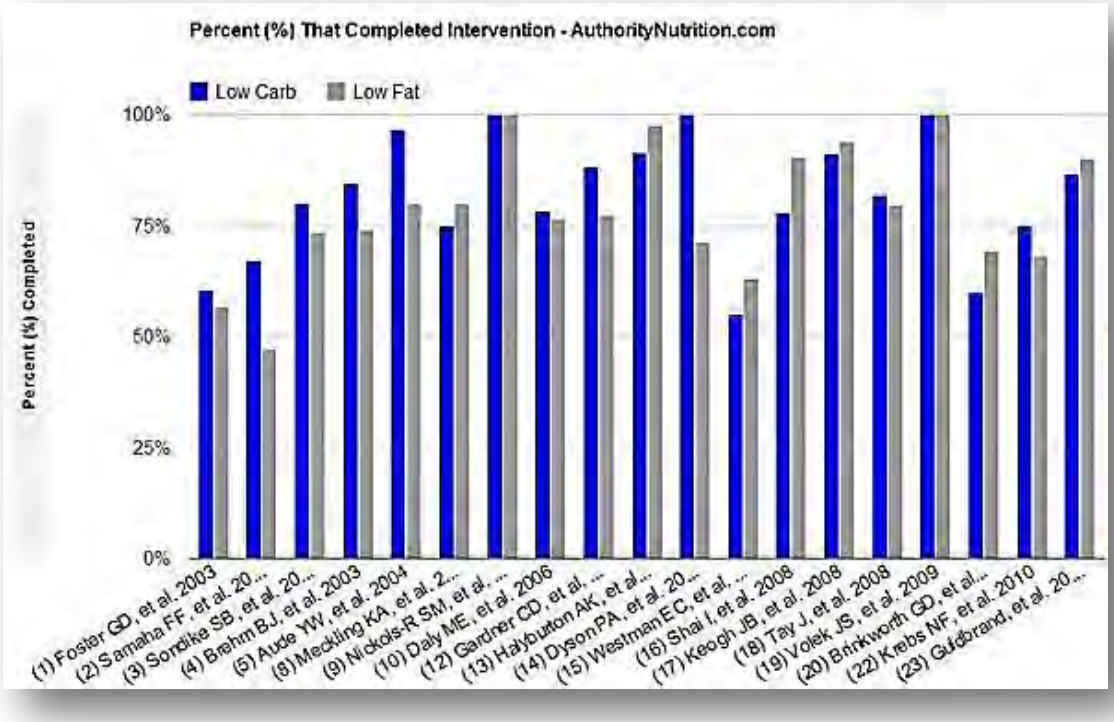
However, the difference was small or nonexistent in the other two studies, because compliance was poor and the individuals ended up eating carbs at about 30% of calories (10, 23).

Blood Pressure

When measured, blood pressure tended to decrease on both low-carb and low-fat diets.

How Many People Made it to The End?

A common problem in weight loss studies is that many people abandon the diet and drop out of the studies before they are completed. I did an analysis of the percentage of people who made it to the end of the study in each group. 19 of the 23 studies reported this number:



The average percentage of people who made it to the end of the studies were:

Average for the low-carb groups: **79,51%**

Average for the low-fat groups: **77,72%**

Not a major difference, but it seems clear from these studies that low-carb diets are at the very least NOT harder to stick to than other diets.

The reason may be that low-carb diets appear to reduce hunger (9, 11) and participants are allowed to eat until fullness.

This is an important point, because low-fat diets are usually calorie restricted and require people to weigh their food and count calories.

Individuals also lose more weight, faster, on low-carb. This may improve motivation to continue on the diet.

Adverse Effects?
Despite the concerns expressed by many health experts in the past, there were **zero reports** of serious adverse effects that were attributable to either diet.

Overall, the low-carb diet was well tolerated and had an outstanding safety profile.

Work – low carbohydrate diet

Complete Scientific.

Long-term effects of a ketogenic diet in obese patients

Hussein M Dashti MD PhD FICS FACS[1], Thazhumpal C Mathew MSc PhD FRCPath[4], Talib Hussein MB ChB[5], Sami K Asfar MB ChB MD FRCSEd FACS[1], Abdulla Behbahani MB ChB FRCS FACSI PhD FICS FACS[1], Mousa A Khoursheed MB ChB FRCS FICS[1], Hilal M Al-Sayer MD PhD FICS FACS[1], Yousef Y Bo-Abbas MD FRCPC[2], Naji S Al-Zaid BSc PhD[3]

HM Dashti, TC Mathew, T Hussein, et al. Long-term effects of a ketogenic diet in obese patients. Exp Clin Cardiol 2004;9(3):200-205.

BACKGROUND: Although various studies have examined the short-term effects of a ketogenic diet in reducing weight in obese patients, its long-term effects on various physical and biochemical parameters are not known.

OBJECTIVE: To determine the effects of a 24-week ketogenic diet (consisting of 30 g carbohydrate, 1 g/kg body weight protein, 20% saturated fat, and 80% polyunsaturated and monounsaturated fat) in obese patients.

PATIENTS AND METHODS: In the present study, 83 obese patients (39 men and 44 women) with a body mass index greater than 35 kg/m^2, and high glucose and cholesterol levels were selected. The body weight, body mass index, total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, fasting blood sugar, urea and creatinine levels were determined before and after the administration of the ketogenic diet. Changes in these parameters were monitored after eight, 16 and 24 weeks of treatment.

RESULTS: The weight and body mass index of the patients decreased significantly ($P<0.0001$). The level of total cholesterol decreased from week 1 to week 24. HDL cholesterol levels significantly increased, whereas LDL cholesterol levels significantly decreased after treatment. The level of triglycerides decreased significantly following 24 weeks of treatment. The level of blood glucose significantly decreased. The changes in the level of urea and creatinine were not statistically significant.

CONCLUSIONS: The present study shows the beneficial effects of a long-term ketogenic diet. It significantly reduced the body weight and body mass index of the patients. Furthermore, it decreased the level of triglycerides, LDL cholesterol and blood glucose, and increased the level of HDL cholesterol. Administering a ketogenic diet for a relatively longer period of time did not produce any significant side effects in the patients. Therefore, the present study confirms that it is safe to use a ketogenic diet for a longer period of time than previously demonstrated.

Key Words: *Diet; Ketosis; Obesity*

Obesity has become a serious chronic disease in both developing and developed countries. Furthermore, it is associated with a variety of chronic diseases (1-4). It is estimated that in the United States alone approximately 300,000 people die each year from obesity-related diseases (5,6). Different methods for reducing weight using reduced calorie and fat intake combined with exercise have failed to show sustained long-term effects (7-9). Recent studies from various laboratories (10,11), including our own (12), have shown that a high fat diet rich in polyunsaturated fatty acids (ketogenic diet) is quite effective in reducing body weight and the risk factors for various chronic diseases. The ketogenic diet was originally introduced in 1920 (13). In this diet, the fat to carbohydrate ratio is 5:1. While there was a significant decrease in the weight of obese patients who were on a ketogenic diet (12), the reverse occurred when the diet changed to one high in carbohydrates (14).

It should be noted that the concept that fat can be eaten ad libitum and still induce weight loss in obese subjects is not a recent one (13-33). Ketosis occurs as a result of the change in the body's fuel from carbohydrate to fat. Incomplete oxidation of fatty acids by the liver results in the accumulation of ketone bodies in the body. A ketogenic diet maintains the body in a state of ketosis, which is characterized by an elevation of D-b-hydroxybutyrate and acetoacetate.

Mild ketosis is a natural phenomenon that occurs in humans during fasting and lactation (19,20). Postexercise ketosis is a well-known phenomenon in mammals. Although most of the changes in the physiological parameters induced following exercise revert back to their normal values rapidly, the level of circulating ketone bodies increases for a few hours after muscular activity ceases (21). It has been found that in trained individuals, a low blood ketone level protects against the development of hypoglycemia during prolonged intermittent exercise (22). In addition, ketosis has a significant influence on suppressing hunger. Thus, a ketogenic diet is a good regulator of the body's calorie intake and mimics the effect of starvation in the body.

It is generally believed that high fat diets may lead to the development of obesity and several other diseases such as coronary artery disease, diabetes and cancer. This view, however, is based on studies carried out in animals that were given a high fat diet rich in polyunsaturated fatty acids. In contrast, our laboratory has recently shown that a ketogenic diet modified the risk factors for heart disease in obese patients (12).

Although various short-term studies examining the effect of a ketogenic diet in reducing the weight of obese patients have been carried out (10), its long-term effects in obese subjects are not known (15). Therefore, the purpose of the present study

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TABLE 1
Patient data at baseline before treatment with the ketogenic diet

	n	Age (years)	Height (m)	Weight (kg)	Body mass index (kg/m^2)
Men	39	42.6±1.7	1.7±0.01	102.4±3.7	35.9±1.2
Women	44	40.6±1.6	1.6±0.01	99.8±2.9	39.4±1.0

All data are mean ± SEM

TABLE 2
Composition of the capsule*

Para-aminobenzoic acid (PH)	30 mg
Vitamin B_1 (thiamin mononitrate) (BP)	15 mg
Vitamin B_2 (riboflavin) (BP)	3 mg
Vitamin B_5 (nicotinamide) (BP)	25 mg
Vitamin B_3 (calcium pantothenate) (PH)	3 mg
Vitamin B_6 (pyridoxine HCl) (BP)	5 mg
Vitamin B_{12} (cyanocobalamin) (BP)	10 µg
Biotin (PH)	5 µg
Folic acid (BP)	100 µg
Vitamin C (ascorbic acid) BP	60 mg
Vitamin A (retinol) (USP; 2000 IU)	0.6 mg
Vitamin D (calciferol) (INN; 200 IU)	5 µg
Vitamin E (tocopherol acetate) (USNF)	10 mg
Lecithin (PH)	40 mg
Wheat germ oil	100 mg
Lysine (FP)	40 mg
Methionine (DAB)	60 mg
Rutin (DAB) (rutoside) (INN)	10 mg
Iron (as fumarate; BP)	12 mg
Calcium (as dicalcium phosphate) (BP)	52 mg
Phosphorus (as dicalcium phosphate) (BP)	40 mg
Potassium (as KCl) (BP)	2 mg
Zinc (as $ZnSO_4$) (BP)	8 mg
Copper (as $CuSO_4$) (BP)	1 mg
Manganese (as $MnSO_4$) (BP)	2 mg
Iodine (as potassium iodide) (BP)	trace
Ginseng (Siberian) (5:1 concentrated extract)	4 mg

**Net weight 45 g. BP British Pharmacopoeia; DAB German Pharmacopoeia; FP French Pharmacopoeia; INN International nonpropietary names; IU International units; PH Swiss Pharmacopoeia; USNF United States National Formulary; USP United States Pharmacopoeia*

was to investigate the long-term effects of a ketogenic diet on obesity and obesity-associated risk factors in a large population of obese patients.

PATIENTS AND METHODS

Patients and biochemical analysis

The prospective study was carried out at the Academic Department of Surgery, Consultation and Training Centre, Faculty of Medicine, Kuwait University (Jabriya, Kuwait) in 83 obese subjects (39 men and 44 women). The body mass index (BMI) of men and women was 35.9±1.2 kg/m^2 and 39.4±1.0 kg/m^2, respectively. The mean age was 42.6±1.7 years and 40.6±1.6 years for men and women, respectively. The mean age, initial height, weight and BMI for all patients are given in Table 1. Fasting blood tests were carried out for all of the subjects. Initially, all patients were subjected to liver and renal function tests, and glucose and lipid profiles, using fasting blood samples, and a complete blood count. Thereafter, fasting blood samples were tested for total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides, blood sugar, urea and creatinine levels at the eighth, 16th and 24th week. In addition, weight and height measurements, and blood pressure were monitored at each visit.

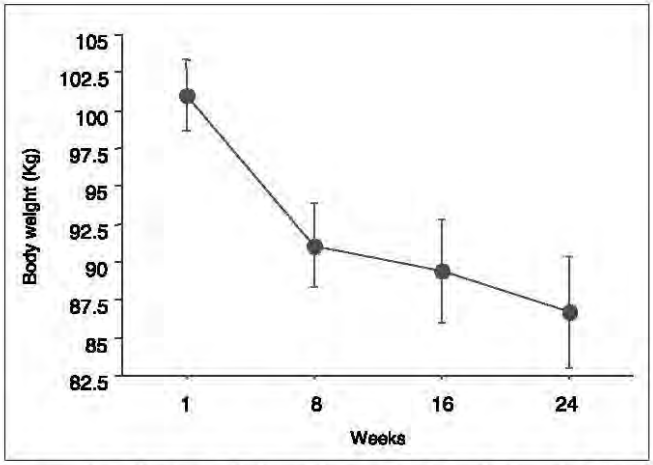

Figure 1) *Reduction in body weight at eight, 16 and 24 weeks following the administration of the ketogenic diet in obese patients. The weights are expressed as mean ± SEM*

Protocol for ketogenic diet-induced body weight reduction

All 83 subjects received the ketogenic diet consisting of 20 g to 30 g of carbohydrate in the form of green vegetables and salad, and 80 g to 100 g of protein in the form of meat, fish, fowl, eggs, shellfish and cheese. Polyunsaturated and monounsaturated fats were also included in the diet. Twelve weeks later, an additional 20 g of carbohydrate were added to the meal of the patients to total 40 g to 50 g of carbohydrate. Micronutrients (vitamins and minerals) were given to each subject in the form of one capsule per day (Table 2).

Statistical analysis

Statistical differences between body weight, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, level of fasting blood sugar, and urea and creatinine levels before and after the administration of the ketogenic diet were analyzed using a paired Student's t test using the Stat-view version 4.02 (Abacus Concepts Inc, USA). Weight, BMI and all biochemical parameters are expressed as mean ± SEM.

RESULTS

The mean initial weight of the subjects was 101.03±2.33 kg. The weight decreased significantly during all stages of the treatment period. The body weights at the eighth, 16th and 24th week were 91.10±2.76 kg, 89.39±3.4 kg and 86.67±3.70 kg, respectively (Figure 1). Similar to the loss in body weight, a significant decrease was observed in the BMI of the patients following the administration of the ketogenic diet. The initial BMI, and the BMI after the eighth, 16th and 24th week were 37.77±0.79 kg/m^2, 33.90±0.83 kg/m^2, 33.24±1.00 kg/m^2 and 32.06±1.13 kg/m^2, respectively (Figure 2).

The level of total cholesterol showed a significant decrease from week 1 to week 24 (Figure 3). The level of HDL cholesterol significantly increased (Figure 4), whereas LDL cholesterol levels significantly decreased with treatment (Figure 5).

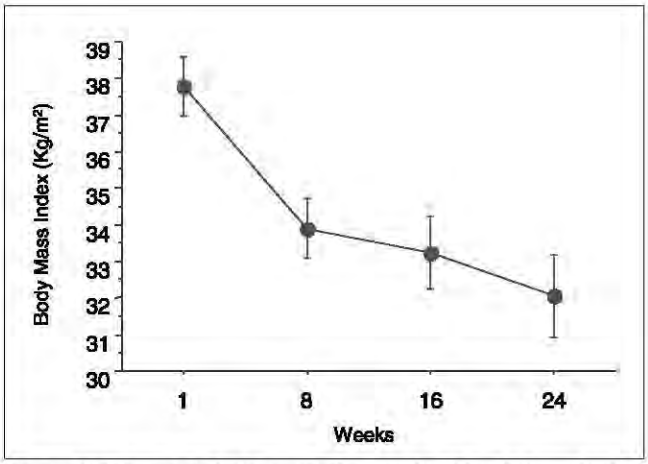

Figure 2) *Decrease in body mass index at eight, 16 and 24 weeks during the administration of a ketogenic diet in obese patients. The values are expressed as mean ± SEM*

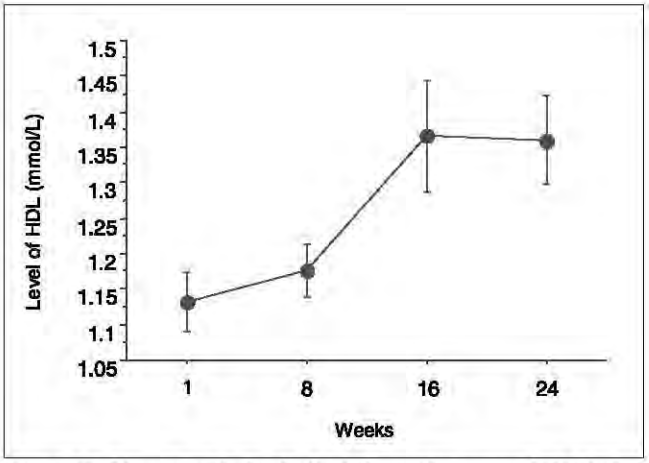

Figure 4) *Changes in the level of high density lipoprotein (HDL) cholesterol in obese patients during treatment with a ketogenic diet for a period of 24 weeks. Data are expressed as mean ± SEM*

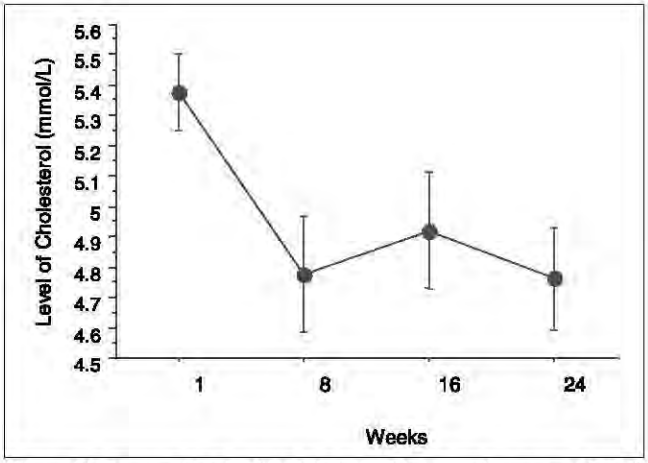

Figure 3) *Decreased levels of total cholesterol (expressed as mean ± SEM) in obese patients at eight, 16 and 24 weeks during the administration of a ketogenic diet*

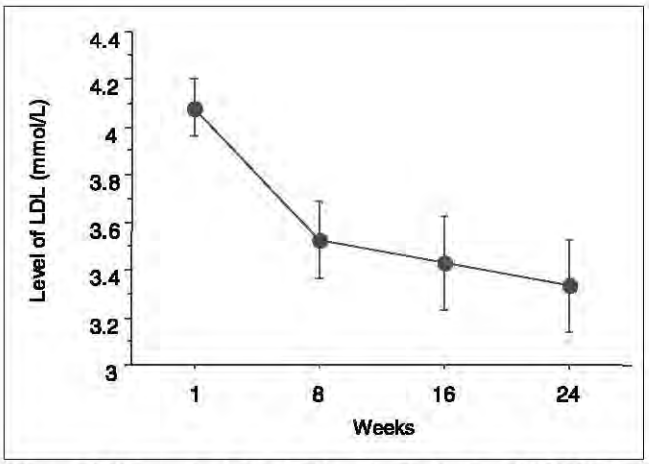

Figure 5) *Changes in the level of low density lipoprotein (LDL) cholesterol during treatment with a ketogenic diet in obese patients at eight, 16 and 24 weeks. The values are expressed as mean ± SEM*

The level of triglycerides decreased significantly after 24 weeks of treatment. The initial level of triglycerides was 2.75±0.23 mmol/L, whereas at week 24, the level decreased to 1.09±0.08 mmol/L (Figure 6). The level of blood glucose significantly decreased at week 24. The initial blood glucose level and its level at the eighth, 16th and 24th week were 7.26±0.38 mmol/L, 5.86±0.27 mmol/L, 5.56±0.19 mmol/L and 5.62±0.18 mmol/L, respectively (Figure 7). The changes in the levels of urea (Figure 8) and creatinine (Figure 9) were not statistically significant.

DISCUSSION

Until recently, ketosis was viewed with apprehension in the medical world; however, current advances in nutritional research have discounted this apprehension and increased public awareness about its favourable effects. In humans, ketone bodies are the only additional source of brain energy after glucose (23,24). Thus, the use of ketone bodies by the brain could be a significant evolutionary development that occurred in parallel with brain development in humans. Hepatic generation of ketone bodies during fasting is essential to provide an alternate fuel to glucose. This is necessary to spare the destruction of muscle from glucose synthesis.

A ketogenic diet is clinically and experimentally effective in antiepileptic and antiobesity treatments; however, the molecular mechanisms of its action remain to be elucidated. In some cases, a ketogenic diet is far better than modern anticonvulsants (25). Recently, it has been shown that a ketogenic diet is a safe potential alternative to other existing therapies for infantile spasms (27). It was further shown that a ketogenic diet could act as a mood stabilizer in bipolar illness (28). Beneficial changes in the brain energy profile have been observed in subjects who are on a ketogenic diet (28). This is a significant observation because cerebral hypometabolism is a characteristic feature of those who suffer from depression or mania (28). It has also been found that a ketogenic diet affects signal transduction in neurons by inducing changes in the basal status of protein phosphorylation (29). In another study (30), it was shown that a ketogenic diet induced gene expression in the brain. These studies provide evidence to explain the actions of a ketogenic diet in the brain.

One of the mechanisms of a ketogenic diet in epilepsy may be related to increased availability of beta-hydroxybutyrate, a ketone body readily transported through the blood-brain barrier. In support of this hypothesis, it was found that a ketogenic diet was the treatment of choice for glucose transporter protein

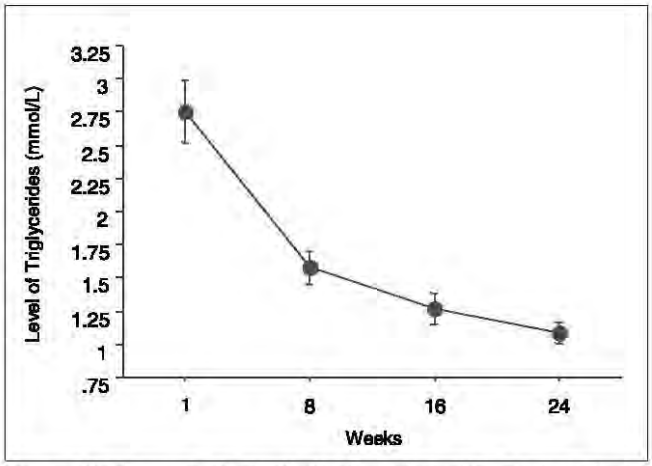

Figure 6) *Changes in the level of triglycerides in obese patients during treatment with a ketogenic diet over a period of 24 weeks. The values are expressed as mean ± SEM*

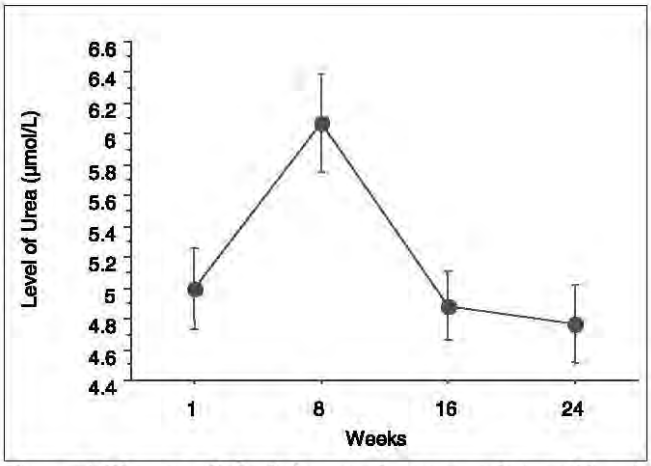

Figure 8) *Changes in the level of urea in obese patients during a 24-week ketogenic diet. The level of urea is expressed as mean ± SEM*

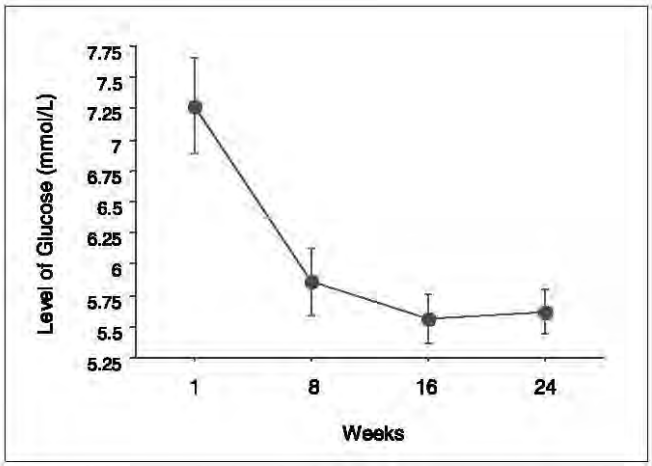

Figure 7) *Decreased levels of blood glucose (expressed as mean ± SEM) in obese patients at eight, 16 and 24 weeks during the administration of a ketogenic diet*

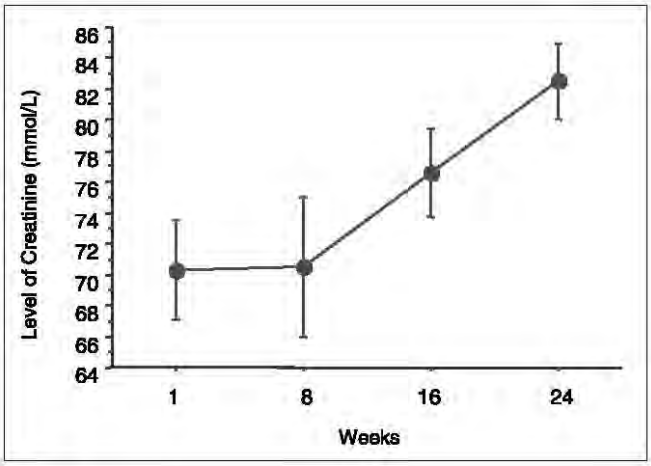

Figure 9) *Changes in the level of creatinine in obese patients during a 24-week ketogenic diet. Values are expressed as mean ± SEM*

syndrome and pyruvate dehydrogenase deficiency, which are both associated with cerebral energy failure and seizures (26).

One argument against the consumption of a high fat diet is that it causes obesity. The major concern in this regard is whether a high percentage of dietary fat promotes weight gain more than a low percentage of fat intake. Because fat has a higher caloric density than carbohydrate, it is thought that the consumption of a high fat diet will be accompanied by a higher energy intake (31). On the contrary, recent studies from our laboratory (12) and many other laboratories (24,32-34) have observed that a ketogenic diet can be used as a therapy for weight reduction in obese patients.

It has been found that a sugary diet is the root cause of various chronic diseases of the body. A recent study (35) showed that sugar can accelerate aging. Several recent studies (36,37) have pointed to the fact that a diet with a high glycemic load is independently associated with the development of cardiovascular diseases, type II diabetes and certain forms of cancer. Glycemic load refers to a diet of different foods that have a high glycemic index. Glycemic index is a measure of the elevation of glucose levels following the ingestion of a carbohydrate. The classification of a carbohydrate based on its glycemic index provided a better predictor of risk for coronary artery diseases than the traditional method of classification of carbohydrate into simple or complex forms (38). In other studies (38-46), it was shown that the risk of dietary glycemic load from refined carbohydrates was independent of other known risk factors for coronary diseases.

It is now evident that high carbohydrate diets increase fasting plasma triglyceride concentrations (47-51) and decrease HDL cholesterol concentrations (52-55). These changes are associated with enhanced atherogenesis (55). However, it has been shown that short-term ketogenic diets improve the lipid disorders that are characteristic of atherogenic dyslipidemia (56). It has also been found that sugary drinks decreased blood levels of vitamin E, thus reducing the amount of antioxidants in the body. It has been proven, beyond a doubt, that disrupting the oxidant-antioxidant status of the cell will lead to various diseases of the body (57).

The relation between a high fat diet and cancer is not conclusive. Recent epidemiological studies (17,58-60) could not explain a specific causal relationship between dietary fat and cancer. It has been found that altered energy metabolism and substrate requirements of tumour cells provide a target for

selective antineoplastic therapy. The supply of substrates for tumour energy metabolism can be reduced by dietary manipulation (eg, ketogenic diet) or by pharmacological means at the cellular level (eg, inhibitors of glycolysis or oxidative phosphorylation). Both of these techniques are nontoxic methods for controlling tumour growth in vivo (61). Sugar consumption is positively associated with cancer in humans and test animals (58-61). This observation is quite logical because tumours are known to be enormous sugar absorbers. It has also been found that the risk of breast cancer decreases with increases in total fat intake (16). Further studies on the role of a ketogenic diet in antineoplastic therapy are in progress in our laboratory.

A link between low fat diets and osteoporosis has been suggested. Very low fat diets are considered to be low in calcium content. Women on low fat diets excrete most of the calcium they consume; therefore, they are more prone to osteoporosis. However, a high fat diet can rectify this situation (62).

In the present study, a control population on a low fat diet was not included due to the difficulties in recruiting subjects for a control group. However, several studies (63,64) with appropriate control groups that compared the effect of a low fat diet with a low carbohydrate ketogenic diet have recently been published. In this regard, these two recent studies are comparable with the present study. Brehm et al (23) showed that obese women on a low carbohydrate ketogenic diet lost 8.5 kg over six months compared with 4.2 kg lost by those in the low fat diet group ($P<0.001$). Twenty-two subjects from the low carbohydrate ketogenic diet and 20 subjects from the low fat diet completed the study, with both groups reducing their energy intake by approximately 450 kcal from the baseline level. In another study performed in 132 severely obese subjects for six months (24), there was greater weight loss in the low carbohydrate ketogenic diet group than in the low fat diet group (5.8 kg versus 1.9 kg, $P=0.002$). Both of these studies support the findings presented in the present paper.

CONCLUSIONS

The data presented in the present study showed that a ketogenic diet acted as a natural therapy for weight reduction in obese patients. This is a unique study monitoring the effect of a ketogenic diet for 24 weeks. There was a significant decrease in the level of triglycerides, total cholesterol, LDL cholesterol and glucose, and a significant increase in the level of HDL cholesterol in the patients. The side effects of drugs commonly used for the reduction of body weight in such patients were not observed in patients who were on the ketogenic diet. Therefore, these results indicate that the administration of a ketogenic diet for a relatively long period of time is safe. Further studies elucidating the molecular mechanisms of a ketogenic diet are in progress in our laboratory. These studies will open new avenues into the potential therapeutic uses of a ketogenic diet and ketone bodies.

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The Journal of Nutrition
Supplement: The Controversial Role of Macronutrient Composition in Diabetes and Related Disorders

A Lower-Carbohydrate, Higher-Fat Diet Reduces Abdominal and Intermuscular Fat and Increases Insulin Sensitivity in Adults at Risk of Type 2 Diabetes[1,3]

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Abstract

Background: Obesity, particularly visceral and ectopic adiposity, increases the risk of type 2 diabetes.

Objective: The aim of this study was to determine if restriction of dietary carbohydrate is benecial for body composition and metabolic health.

Methods: Two studies were conducted. In the rst, 69 overwei ght/obese men and women, 53% of whom were European American (EA) and 47% of whom were African American (AA), were provided with 1 of 2 diets (lower-fat diet: 55%, 18%, and 27% of energy from carbohydrate, protein, and fat, respectively; lower-carbohydrate diet: 43%, 18%, and 39%, respectively) for 8 wk at a eucaloric level and 8 wk at a hypocaloric level. In the second study, 30 women with polycystic ovary syndrome (PCOS) were provided with 2 diets (lower-fat diet: 55%, 18%, and 27% of energy from carbohydrate, protein, and fat, respectively; lower-carbohydrate diet: 41%, 19%, and 40%, respectively) at a eucaloric level for 8 wk in a random-order crossover design.

Results: As previously reported, among overweight/obese adults, after the eucaloric phase, participants who consumed the lower-carbohydrate vs. the lower-fat diet lost more intra-abdominal adipose tissue (IAAT) (11 ± 3% vs. 1 ± 3%; $P < 0.05$). After weight loss, participants who consumed the lower-carbohydrate diet had 4.4% less total fat mass. Original to this report, across the entire 16-wk study, AAs lost more fat mass with a lower-carbohydrate diet (6.2 vs. 2.9 kg; $P < 0.01$), whereas EAs showed no difference between diets. As previously reported, among women with PCOS, the lower-carbohydrate arm showed decreased fasting insulin (−2.8 μIU/mL; $P < 0.001$) and fasting glucose (−4.7 mg/dL; $P < 0.01$) and increased insulin sensitivity (1.06 arbitrary units; $P < 0.05$) and dynamic β-cell response (96.1 10^9; $P < 0.001$). In the lower-carbohydrate arm, women lost both IAAT (−4.8 cm^2; $P < 0.01$) and intermuscular fat (−1.2 cm^2; $P < 0.01$). In the lower-fat arm, women lost lean mass (−0.6 kg; $P < 0.05$). Original to this report, after the lower-carbohydrate arm, the change in IAAT was positively associated with the change in tumor necrosis factor α ($P < 0.05$).

Conclusion: A modest reduction in dietary carbohydrate has benecial effects on body composition, fat distribution, and glucose metabolism. This trial was registered at clinicaltrials.gov as NCT00726908 and NCT01028989. *J Nutr* 2015;145:177S83S.

Keywords: insulin secretion, insulin sensitivity, PCOS, glycemic load, visceral fat, body composition

Introduction

Obesity, particularly intra-abdominal and ectopic adiposity, is associated with insulin resistance. Insulin resistance, in combination with β cell dysfunction, contributes to the development of type 2 diabetes (T2D)[4] (1). To address the current worldwide increase in T2D prevalence, feasible nonpharmacologic approaches are needed for preventing and reversing obesity and obesity-related metabolic dysfunction.

The consumption of large amounts of processed carbohydrate-containing foods may be one of the major factors leading to both

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[4] Abbreviations used: AA, African American; AIRg, acute insulin response to glucose; CRP, C-reactive protein; CT, computed tomography; EA, European American; IAAT, intra-abdominal adipose tissue; IMAT, intermuscular adipose tissue; PCOS, polycystic ovary syndrome; PhID, dynamic phase serum insulin response to glucose; T2D, type 2 diabetes.

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obesity and metabolic dysfunction. The consumption of processed carbohydrates leads to elevated insulin secretion, which, in turn, promotes glucose oxidation, impairs fat oxidation, facilitates de novo lipogenesis, and promotes storage of fat (2), while at the same time leading to insulin resistance, inammation (3), and oxidative stress (4). The combination of insulin resistance and hyperinsulinemia also disrupts lipid metabolism and increases the risk of cardiovascular disease, the most common source of mortality among individuals with T2D (5).

In contrast, when dietary carbohydrate is restricted and insulin declines, metabolic processes shift to favor fat oxidation over lipid storage. As a result, the lipid prole improves, and lipotoxic processes that impairβcell function and insulin action resolve. A number of studies documented the benets of lower-carbohydrate diets on measures of metabolic health and medication use in patients with T2D (611) and for weight loss and improved metabolic health in healthy individuals (12). Despite these well-documented benets, carbohydrate restriction or reduction is not currently recommended for prevention or treatment of diabetes by the major organizations and institutions to which physicians turn for guidance (13, 14).

The impact of dietary carbohydrate on metabolism may differ with individual phenotype. We and others have reported that the degree of insulin sensitivity and the amount of insulin secreted after a glucose challenge affect the extent to which dietary carbohydrate quantity and quality affect the change in body weight and body composition over 1218 mo (1518). Individuals who are more sensitive to insulin, or who secrete a greater amount of insulin in response to a glucose challenge, appear to be more sensitive to the stimulatory effects of dietary carbohydrate on fat deposition. These observations may be particularly relevant to ethnic minorities. African Americans (AAs), Mexican Americans, and Native Americans secrete a greater amount of insulin than do European Americans (EAs) for a given amount of exposure to oral or intravenous glucose (19 21). All of these minority groups are at greater risk of both obesity and T2D compared with EAs. Thus, although it is possible that diet modication could play a particularly relevant role in improving metabolic health in ethnic minorities, this hypothesis has not been tested.

This article discusses the results of 2 recent studies comparing carbohydrate-restricted diets with lower-fat diets in 2 populations at elevated risk of T2D. In both studies, the 2 experimental diets were matched for protein content to avoid potential confounding effects of altered protein intake on body composition or metabolic outcomes. The rst study, conducted in nondiabetic but overweight or obese AA and EA adults, examined body composition and body fat distribution during conditions of both weight maintenance and weight loss. The second study, conducted in women with polycystic ovary syndrome (PCOS), examined these outcomes as well as outcomes related to metabolic health (insulin sensitivity and β cell function) during weight maintenance. Women with PCOS are characterized by insulin resistance, hyperinsulinism, and perhaps visceral adiposity (2224) and are therefore at increased risk of T2D.

Methods

Overweight/obese adults. Sixty-nine men and women aged 2150 y were enrolled in the study. Details of the study were published previously (2527). Briey, inclusion criteria were BMI (in kg/m ^{2}) of 2545, weight <136 kg, age 2150 y, nondiabetic, and no weight change of >2.3 kg over the past 6 mo. Approximately 50% of participants were AAs and ~50% were EAs, by design, to examine potential differences in the response to diet on the basis of ethnicity. Glucose tolerance was evaluated at screening by using a 2-h oral-glucose-tolerance test, and only those who had 2-h glucose in the normal or mildly impaired range (≤155 mg/dL) were eligible for the study. Twenty-seven participants had impaired fasting glucose (≥100 mg/dL). Participants were informed of the experimental design, and oral and written consent was obtained. The study was approved by the Institutional Review Board for Human Use at the University of Alabama at Birmingham.

Baseline testing included body composition by DXA, body fat distribution by computed tomography (CT) scan, and the acute insulin response to glucose (AIRg). AIRg is the incremental AUC for insulin during the rst 10 min after intravenous glucose injection at a dose of 300 mg/kg. After completing baseline testing, participants were assigned to 1 of 2 diets that differed in percentage of energy from carbohydrate (55% or 43%) and fat (27% or 39%), with both having 18% protein, and were provided with all food at a eucaloric level for an 8-wk period. At week 4, participants were administered a breakfast meal test (28). For this test, blood was collected before and for 4 h during and after consumption of a breakfast meal that was part of their assigned diet. Serum concentrations of insulin and glucose were assessed at several time points. After completion of the 8-wk eucaloric period, participants entered a second 8-wk intervention period in which energy intake was decreased by 1000 kcal/d. Body composition and fat distribution were assessed at the end of both eucaloric and hypocaloric phases. Data were analyzed within all participants combined, and within each ethnic group.

Original to this report, circulating markers of inammation were assessed by immunoassay in fasted morning sera before and after the intervention. High-sensitivity C-reactive protein (CRP) was assessed by turbidometric methods by using a SIRRUS analyzer (Stanbio Laboratory), with reagents obtained from Pointe Scientic, and TNF- αand IL-6 by using electrochemiluminscence (Meso Scale Discovery). Minimum detectable concentrations for each assay were 0.05 mg/L, 0.507 pg/mL, and 0.25 pg/mL, respectively. Mean intra-assay CVs were 7.49%, 7.61%, and 6.68%, respectively. Mean interassay CVs were 2.13%, 5.47%, and 9.72%, respectively. Data were analyzed by paired$t$test and by ANCOVA for the main outcome of 8-wk concentration, with baseline concentration as a covariate. In addition, to determine if changes in intra-abdominal adipose tissue (IAAT) were associated with changes in markers of inammation, multiple linear regression analysis was conducted within each diet group to adjust for the change in total body fat mass. All analyses were conducted with the use of SAS software (version 9.3; SAS Institute); theαlevel was set at 0.05.

Original to this report, data were analyzed within each ethnic group. Because AAs relative to EAs have a greater insulin response to glucose, it was of interest to determine if the response to dietary carbohydrate content differed in AAs vs. EAs. For these analyses, data from the entire 16-wk intervention were combined. Preliminary analyses indicated that because some participants lost weight and fat during the eucaloric phase, the body composition response to the entire 16-wk intervention gave the clearest picture of how the change in diet macronutrient composition affected body composition. Thus, the change in body fat mass (kg) was assessed by using ANCOVA, with fat mass at 16 wk as the dependent variable, ethnicity as the class variable, and baseline fat mass and insulin sensitivity as covariates. Insulin sensitivity was selected as a covariate because it interacts with diet composition in determining changes in body composition over time (15, 16). The least squares means procedure was used to generate adjusted means and SEMs for graphical presentation. All analyses were conducted by using SAS software (version 9.3); the α level was set at 0.05. Descriptive statistics are presented as means ± SDs; main outcome data are presented as means ± SEMs.

Women with PCOS. Details of the study were published previously (29). Briey, 30 women with PCOS were enrolled in the study. Participants were informed of the experimental design, and oral and written consent was obtained. The study was approved by the Institutional Review Board for Human Use at the University of Alabama at Birmingham.

The study was conducted by using a crossover design. Comprehensive metabolic testing was conducted before and after each 8-wk arm, with a 4-wk washout period between arms. After completing baseline testing, participants were assigned, by using a randomization scheme, to

1 of 2 diets: a lower-fat diet with a macronutrient composition of 55% carbohydrate, 18% protein, and 27% fat (% of energy from each) or a lower-carbohydrate diet with a macronutrient composition of 41% carbohydrate, 19% protein, and 40% fat. All food was provided for the duration of each arm.

Dynamicβ cell response to glucose [dynamic phase serum insulin response to glucose (PhiD)] was determined before and after each diet arm by using glucose and C-peptide data obtained during a liquid meal tolerance test (30). Insulin sensitivity was calculated by using a formula based on insulin and glucose values throughout the meal test (31). Original to this report, circulating markers of inammation were assessed by immunoassay as described in the previous section, Overweight/obese adults. Body composition by DXA and body fat distribution by CT scan were determined before and after each arm. Cross-sectional areas of IAAT and intermuscular adipose tissue (IMAT) were quantied from CT scans by using SliceOmatic software (TomoVision).

Main outcomes were fasting glucose, fasting insulin, insulin sensitivity,βcell responsiveness, body composition, and body fat distribution. Secondary outcomes were circulating markers of inammation. Data were analyzed by pairedttest for changes within each treatment arm and by ANCOVA for differences between diet arms ($\alpha = 0.05$). Descriptive statistics are presented are means ± SDs; main and secondary outcome data are presented as means±SEMs. To determine if changes in IAAT were independently associated with changes in markers of inammation, multiple linear regression analysis was conducted within each diet group for the dependent variable change in CRP/TNF-α/IL-6, with changes in IAAT and total body fat mass as independent variables.

Results

Overweight/obese adults. Descriptive characteristics of the study population, by ethnicity, are shown in**Table 1.** AA and EA participants did not differ with respect to age, BMI, or fat mass. However, AAs had 40% greater AIRg ($P< 0.01$).

As previously reported (27), in the eucaloric phase, loss of IAAT was signicantly greater ($P < 0.05$; **Figure 1**A) in participants who consumed the lower-carbohydrate diet (11%) than in those who consumed the lower-fat diet. Furthermore, when comparing the 2 diet groups at the end of the eucaloric phase, participants who consumed the lower-carbohydrate diet had 11% less intra-abdominal fat (IAAT) than did those who consumed the lower-fat diet ($P < 0.05$, adjusted for total fat mass and baseline IAAT). In the hypocaloric phase, total fat mass loss was greater in participants who consumed the lower-carbohydrate (4.4%) diet vs. those who consumed the lower-fat diet ($P < 0.05$; Figure 1B). Original to this report, markers of inammation did not change in response to either of the diets ($P > 0.05$) when data were analyzed by paired t test or ANCOVA (**Table 2**). Furthermore, changes in markers of inammation were not associated with the change in IAAT. Original to this report, over the course of the entire study, loss of total body fat was greater in AAs, but not EAs, in individuals receiving the lower-carbohydrate diet (**Figure 2**).

Results from the breakfast meal test at 4 wk indicated that the insulin response to the 2 diets differed, with peak insulin concentration ($P< 0.05$) and incremental insulin AUC ($P< 0.01$) being signicantly lower after the lower-carbohydrate breakfast meal (**Figure 3**) (28). AUC glucose did not differ between the 2 meals; however, serum glucose concentration was lower at 3 and 4 h during the lower-fat meal ($P< 0.05$).

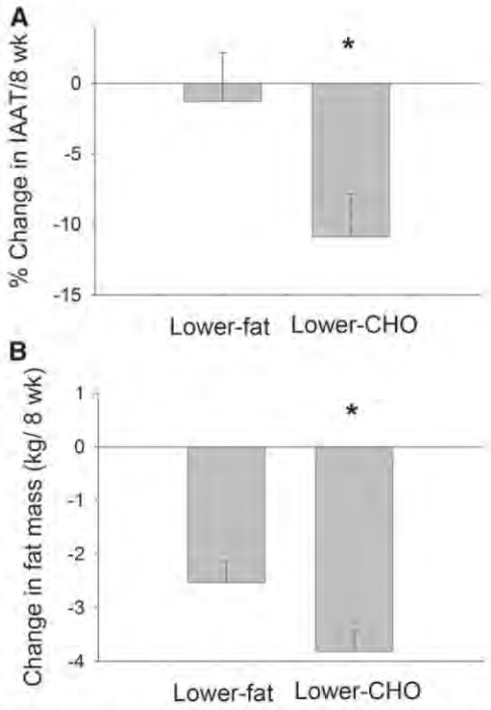

FIGURE 1 Change in IAAT over 8 wk during the eucaloric phase (A) and in total fat mass over 8 wk during the hypocaloric phase (B) in overweight/obese adults consuming a lower-CHO or lower-fat diet. Values are means ±SEMs. A: Lower-fat diet, $n = 29$; lower-carbohydrate diet,$n = 34$; B: lower-fat diet, $n = 28$; lower-CHO diet, $n = 31$. *Different from lower-fat arm, $P< 0.05$. Both panels were adapted from reference 27. CHO, carbohydrate; IAAT, intra-abdominal adipose tissue.

TABLE 1 Participant characteristics by ethnicity among overweight/obese adults[1]

	EA	AA
Sex (M/F),*n*	18/18	13/20
BMI, kg/m^2	31.8±3.7	33.2±4.7
Age, y	36.1±8.0	34.1±8.6
Weight, kg	97.2±18.5	102.0±19.0
Fat mass, kg	38.9±9.2	40.6±8.8
AIRg,μ IU/mL ×10 min	824±628	1420±917**

[1] Values are means ± SDs; $n = 36$ EAs, $n = 33$ AAs. **Different from EAs, $P< 0.01$. AA, African American; AIRg, acute insulin response to glucose; EA, European American.

TABLE 2 Serum concentrations of markers of inammation at baseline and at 8 wk in overweight/obese adults and women with PCOS consuming lower-fat and lower-CHO diets[1]

	Lower-fat diet		Lower-CHO diet	
	Week 0	Week 8	Week 0	Week 8
Overweight/obese adults				
CRP, mg/L	0.46±0.06	0.45±0.07	0.66±0.05	0.58±0.06
TNF-α, pg/mL	0.95±0.01	0.94±0.01	0.96±0.02	0.94±0.02
IL-6, pg/mL	0.40±0.02	0.38±0.02	0.45±0.02	0.42±0.02
Women with PCOS				
CRP, mg/L	0.68±0.06	0.67±0.08	0.65±0.06	0.66±0.06
TNF-α, pg/mL	0.80±0.03	0.78±0.02	0.74±0.03	0.75±0.02
IL-6, pg/mL	0.46±0.03	0.41±0.04	0.39±0.03	0.39±0.03

[1] Values are means ± SEMs. For overweight/obese adults (parallel-arm design): lower-fat diet,$n = 26$; lower-CHO diet, $n = 36$; for women with PCOS (crossover design): lower-fat diet,$n = 23$; lower-CHO diet, $n = 27$. CHO, carbohydrate; CRP, C-reactive protein; PCOS, polycystic ovary syndrome.

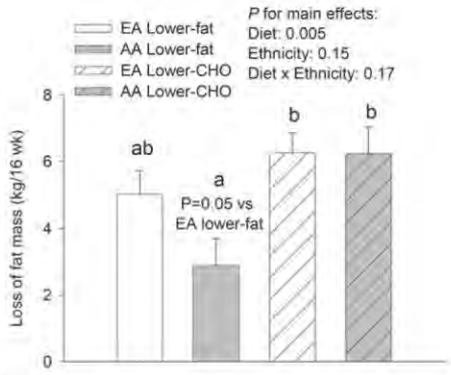

FIGURE 2 Loss of total body fat over 16 wk (8 wk eucaloric followed by 8 wk 1000-kcal/d energy deficit) in overweight/obese AA and EA adults consuming a lower-CHO or lower-fat diet. Values are means ± SEMs. EA lower-fat diet arm, n = 14; AA lower-fat arm, n = 14; EA lower-CHO arm, n = 18, AA lower-CHO arm, n = 13. Different lowercase letters indicate significant differences between groups. Within AAs, those who consumed the lower-CHO diet lost more fat than did those consuming the lower-fat diet ($P < 0.05$). Within the lower-fat diet groups, the difference between ethnic groups in fat loss was significant at $P = 0.05$. AA, African-American; CHO, carbohydrate; EA, European-American.

Women with PCOS. Participant characteristics at baseline are shown in **Table 3**. As reported previously (29), a paired *t* test indicated that the lower-carbohydrate diet resulted in signicant decreases in fasting insulin ($P < 0.001$) and fasting glucose ($P < 0.01$) and signicant increases in insulin sensitivity ($P < 0.05$) and PhiD ($P < 0.001$) (**Figure 4**). No changes in these outcomes were observed while consuming the lower-fat diet. Original to this report, markers of inammation did not change in response to either of the diets (Table 2). However, after the lower-carbohydrate arm, the change in IAAT was associated with the change in TNF-α (standardized coefcient = 0.45, $P = 0.04$) independent of the change in total body fat mass.

As previously reported (32), while in the lower-carbohydrate arm, women lost both IAAT ($P < 0.01$) and IMAT ($P < 0.01$). In contrast, while in the lower-fat arm, women lost lean mass ($P < 0.05$) (**Figure 5**). No changes in IAAT or IMAT were observed during the lower-fat arm, and no change in lean mass was observed over the course of the lower-carbohydrate arm. Although loss of total fat mass was signicant with both diets, it was greater with the lower-carbohydrate diet ($P < 0.05$; adjusted for baseline total fat mass and change in lean mass).

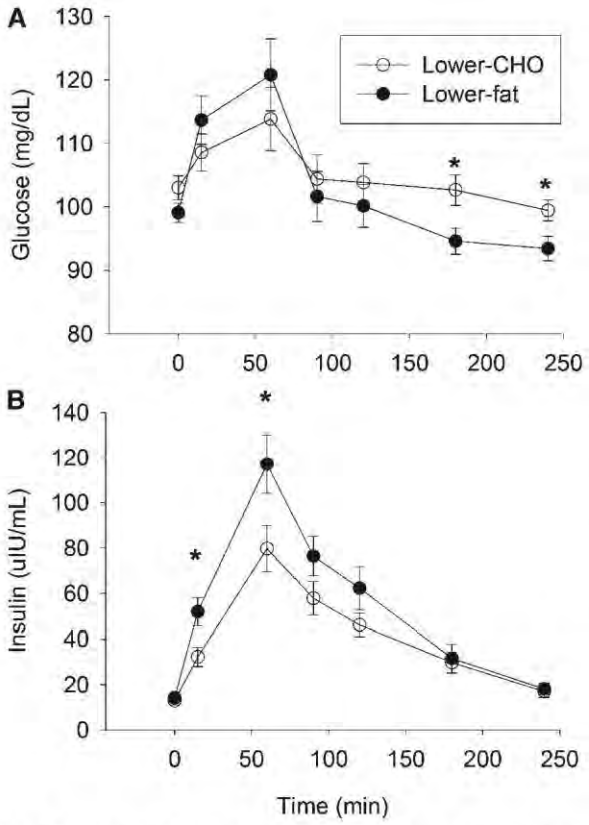

FIGURE 3 Serum glucose (A) and insulin (B) concentrations in overweight/obese adults after consumption of lower-CHO or lower-fat breakfast meals. Values are means± SEMs. *Groups differ at that time, $P < 0.05$. Lower-fat diet, n = 29; lower-CHO diet, n = 35. Adapted from reference 28 with permission. CHO, carbohydrate.

TABLE 3 Characteristics of participants in the PCOS study at baseline[1]

Characteristic	Value
BMI, kg/m^2	31.8± 5.7
Age, y	31.2± 5.8
Serum analytes	
Fasting glucose, mg/dL	96.0± 9.0
Fasting insulin, μIU/mL	8.6± 6.6
Testosterone, ng/dL	53.7±28.3
SHBG, nmol/L	49.3±21.0
FAI	4.3± 2.8

[1] Values are means ± SDs; n = 30. Adapted from reference 29 with permission. FAI, Free Androgen Index [(total testosterone in nmol/L/SHBG in nmol/L) × 100]; PCOS, polycystic ovary syndrome; SHBG, sex hormone binding globulin.

Discussion

Among nondiabetic, overweight/obese adults, we found that the consumption of a lower-carbohydrate vs. a lower-fat diet resulted in selective depletion of IAAT during weight-maintenance conditions and enhanced depletion of total body fat under weight-loss conditions. Insulin response to a breakfast test meal was lower with the lower-carbohydrate diet (when compared with the lower-fat diet). These observations suggest that carbohydrate restriction reduces insulin secretion, which may facilitate fat mobilization (33), particularly from the intra-abdominal area, a depot associated with metabolic dysfunction that is enlarged in individuals with T2D (34, 35).

Although IAAT is considered a proinammatory adipose depot, we did not observe changes in markers of inammation over the course of the intervention, regardless of diet assignment. Nor did we observe a correlation between changes in IAAT and changes in markers of inammation. In a previous study that involved weight loss with the use of a hypocaloric prescription, we observed decreases in all markers of inammation assessed, with the decrease in TNF-αbest explained by the decrease in IAAT (36). Furthermore, on a cross-sectional basis, TNF-αwas associated with IAAT but not with total fat mass or any other individual fat depot (37). On the basis of the observation that dietary carbohydrates have proinammatory effects (3, 38), we anticipated that the lower-carbohydrate diet would reduce inammation either directly or via depletion of IAAT. It is possible that our lower-carbohydrate prescription (43% carbohydrate) was not sufciently low to reduce inammation or that the greater amount of saturated fat (1213%) in this diet

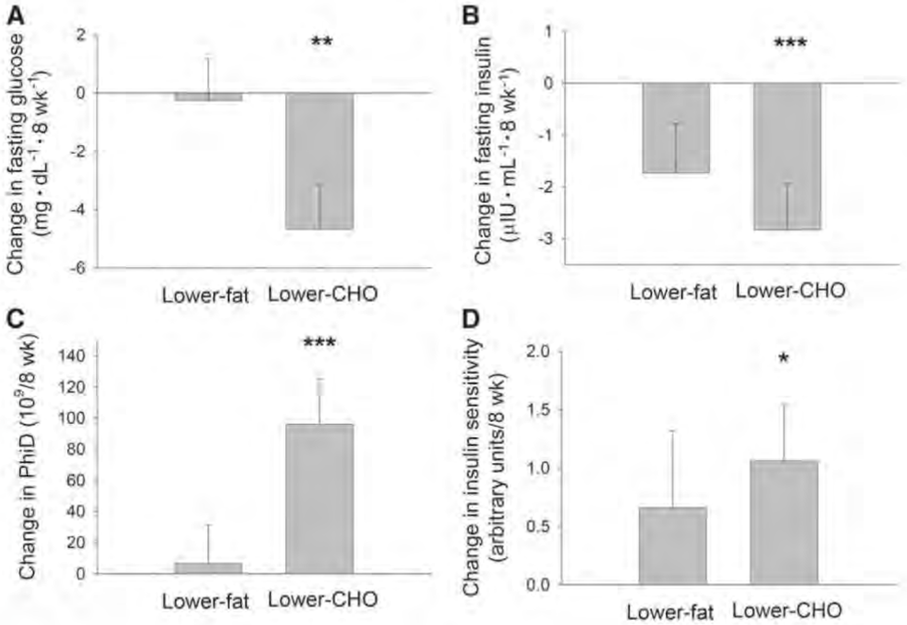

FIGURE 4 Changes in fasting serum glucose (A), fasting serum insulin (B), PhiD (C), and insulin sensitivity (D) from baseline to week 8 in women with polycystic ovary syndrome who consumed lower-CHO and lower-fat diets. Values are means ± SEMs. Lower-fat diet, n = 23; lower-CHO diet, n = 27. Different from baseline: *P<0.05, **P<0.01, ***P< 0.001. Adapted from reference 29 with permission. CHO, carbohydrate; PhiD, dynamic phase serum insulin response to glucose.

negated any potentially benecial effect of carbohydrate reduction. It will be important in future studies to identify the aspects of diet composition that minimize inammation.

We also observed that the loss of body fat with carbohydrate (vs. fat) restriction was greater among AA individuals, a group characterized by a strikingly high AIRg. We previously observed that insulin-sensitive AA women who consumed a diet relatively high in glycemic load showed greater gain in body fat under free-living conditions (16). This phenotype-by-diet interaction was not observed in EA women. It is tempting to speculate that the greater insulin responsiveness of AAs contributes to their sensitivity to diet composition. Specically, that dietary carbohydrate, by altering insulin secretion, affects insulin-stimulated deposition of lipid in adipose tissue. Prospective studies are needed to examine the interactive effects of insulin sensitivity, insulin secretion, and diet composition on change in body composition in AAs and EAs. It is possible that diets individually tailored to specic phenotypes would result in greater success with both weight loss and weight-loss maintenance, particularly for ethnic minorities who are at elevated risk of both obesity and T2D.

In women with PCOS, a lower-carbohydrate diet intervention resulted in decreases in fasting glucose and fasting insulin and a concomitant improvement in insulin sensitivity. We also observed an increase in rst-phase βcell response (PhiD). A low or inadequate rst-phase βcell response is one of the rst signs of impaired β cell function (39) and appears to occur due to glucose toxicity (4043). In the current study, the reduction in fasting glucose observed with the lower-carbohydrate diet may have permitted the increase in PhiD.

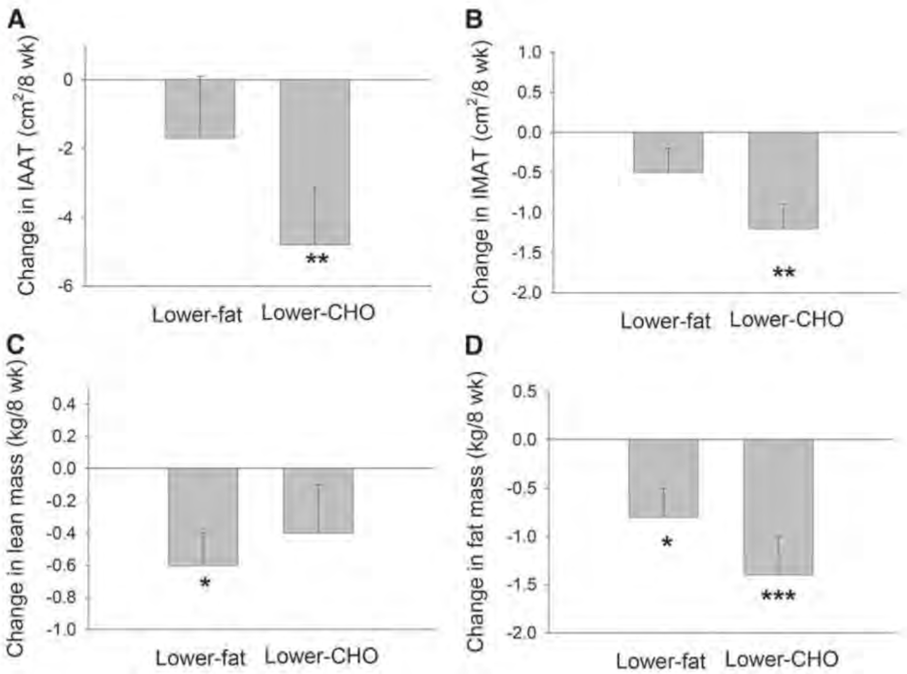

FIGURE 5 Changes in IAAT (A), IMAT (B), total body lean mass (C), and total body fat mass (D) from baseline to week 8 in women with polycystic ovary syndrome who consumed lower-CHO and lower-fat diets. Values are means ± SEMs. Lower-fat diet, n = 23; lower-CHO diet, n = 27. Different from baseline: *P < 0.05, **P < 0.01, ***P< 0.001. Adapted from reference 32 with permission. CHO, carbohydrate; IAAT, intra-abdominal adipose tissue; IMAT, intermuscular adipose tissue.

PCOS is one of the most common endocrine disorders in premenopausal women (44). Although its etiology is not entirely clear, it is thought that a genetic predisposition to insulin resistance of skeletal muscle leads to an elevation in insulin secretion that stimulates testosterone production from the ovaries, which remain sensitive to insulin action. Infertility, hirsutism, and obesity are characteristics of the disorder. In addition, women with PCOS are at elevated risk of developing both T2D and cardiovascular disease, presumably due to their insulin resistance and hyperinsulinism. Although treatment with oral contraceptives and other drugs that alter the reproductive-endocrine axis can alleviate symptoms, there is a need for nonpharmacologic treatment options. That diet modication through carbohydrate restriction could alleviate symptoms by lowering insulin secretion is a possibility worth pursuing.

Women with PCOS also showed favorable changes in body composition (lower fat mass and preservation of lean mass) and fat distribution (lower IAAT and IMAT) with the lower-carbohydrate diet. These changes would be expected to improve metabolic health. The role of IMAT in the etiology of chronic metabolic disease has not been widely investigated. However, greater IMAT was observed in men with T2D and has been associated with greater prevalence of hyperglycemia (45). Furthermore, greater IMAT has been associated with elevation in markers of inammation (46). These observations suggest that fatty inltration of skeletal muscle is either a contributor to, or a marker of, impaired metabolic health.

Overweight women with PCOS have been characterized by elevated markers of inammation relative to weight-matched healthy controls (4749). Markers of inammation are inversely associated with insulin sensitivity (37), and elevated biomarkers of inammation are a risk factor for T2D (50). Thus, we predicted that a diet that improved metabolic health would result in a reduction in circulating markers of inammation. In support of this hypothesis, we observed that after the lower-carbohydrate arm, the change in IAAT was associated with the change in TNF-α, independent of the change in total body fat mass. This observation suggests that depletion of IAAT with carbohydrate restriction may have mediated a decrease in inammation. In women with or without PCOS, in vitro TNF- α production was correlated with circulating concentrations of testosterone and androstenedione (51). It is possible that the decrease in testosterone observed in this study after the lower-carbohydrate diet (29) may have been related to inammation. Longer-term studies are needed to better gauge the effectiveness of carbohydrate restriction in reducing inammation and associated reproductive and metabolic defects in women with PCOS.

A strength of both studies was that the protein content of the diets did not differ. Elevated dietary protein may contribute to maintenance of, or gain in, lean body mass (52). In addition, dietary protein affects insulin secretion (53) and satiety (54). Because we were assessing the inuence of carbohydrate reduction on insulin secretion, we wanted to avoid any potential confounding inuence of differences in dietary protein. We provided food throughout the study; thus, we did not anticipate that differences in satiety/hunger would affect study results, because food intake was determined by the study protocol. However, one of the goals of the studies was to evaluate the effect of the diets on hunger/satiety (28). For this reason, the protein content of the 2 diets was carefully matched.

In summary, among 2 groups of individuals at elevated risk of T2D (overweight/obese/prediabetic adults, women with PCOS), restriction of dietary carbohydrate (relative to restriction of dietary fat) resulted in favorable changes in body composition, fat distribution, and glucose metabolism that may reduce the risk of T2D.

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ORIGINAL ARTICLE

A Randomized Trial of a Low-Carbohydrate Diet for Obesity

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ABSTRACT

BACKGROUND

Despite the popularity of the low-carbohydrate, high-protein, high-fat (Atkins) diet, no randomized, controlled trials have evaluated its efficacy.

METHODS

We conducted a one-year, multicenter, controlled trial involving 63 obese men and women who were randomly assigned to either a low-carbohydrate, high-protein, high-fat diet or a low-calorie, high-carbohydrate, low-fat (conventional) diet. Professional contact was minimal to replicate the approach used by most dieters.

RESULTS

Subjects on the low-carbohydrate diet had lost more weight than subjects on the conventional diet at 3 months (mean [–SD], –6.8–5.0 vs. –2.7–3.7 percent of body weight; P=0.001) and 6 months (–7.0–6.5 vs. –3.2–5.6 percent of body weight, P=0.02), but the difference at 12 months was not significant (–4.4–6.7 vs. –2.5–6.3 percent of body weight, P=0.26). After three months, no significant differences were found between the groups in total or low-density lipoprotein cholesterol concentrations. The increase in high-density lipoprotein cholesterol concentrations and the decrease in triglyceride concentrations were greater among subjects on the low-carbohydrate diet than among those on the conventional diet throughout most of the study. Both diets significantly decreased diastolic blood pressure and the insulin response to an oral glucose load.

CONCLUSIONS

The low-carbohydrate diet produced a greater weight loss (absolute difference, approximately 4 percent) than did the conventional diet for the first six months, but the differences were not significant at one year. The low-carbohydrate diet was associated with a greater improvement in some risk factors for coronary heart disease. Adherence was poor and attrition was high in both groups. Longer and larger studies are required to determine the long-term safety and efficacy of low-carbohydrate, high-protein, high-fat diets.

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AT ANY GIVEN TIME, APPROXIMATELY 45 percent of women and 30 percent of men in the United States are trying to lose weight.[1] Despite these efforts, the prevalence of obesity has doubled in the past 20 years[2] and has become a major public health problem.[3] The conventional dietary approach to weight management, recommended by the leading research and medical societies,[4-7] is a high-carbohydrate, low-fat, energy-deficit diet. Low-carbohydrate, high-protein, high-fat diets have become increasingly popular, and many best-selling diet books have promoted this approach.[8,9] The Atkins diet, originally published in 1973 and again in 1992 and 2002, may be the most popular of these diets. More than 10 million copies of Atkins's diet book have been sold,[10] and four times as many dieters have read one of the Atkins books as have read any other diet book.[11]

Despite its longevity and popularity, no randomized trials evaluating the efficacy of the Atkins diet have been published.[12,13] Data from short-term, uncontrolled studies indicate that the Atkins diet induces weight losses of 8.3 percent after 8 weeks[14] and 10.3 percent after 24 weeks.[15]

We conducted a one-year, multicenter, randomized, controlled trial to evaluate the effect of the low-carbohydrate, high-protein, high-fat Atkins diet on weight loss and risk factors for coronary heart disease in obese persons. The subjects were randomly assigned to follow either a low-carbohydrate, high-protein, high-fat Atkins diet or a high-carbohydrate, low-fat, energy-deficit conventional diet. Professional contact was minimal, so as to approximate the approach used by most dieters.

METHODS

SUBJECTS

A total of 63 persons (43 women and 20 men) participated in the study (Table 1). All subjects completed a comprehensive medical examination and routine blood tests. Potential subjects were excluded if they had clinically significant illnesses, including type 2 diabetes; were taking lipid-lowering medications; were pregnant or lactating; or were taking medications that affect body weight. All subjects provided written informed consent, and the protocol was approved by the institutional review boards of the participating institutions.

STUDY DESIGN

The subjects were randomly assigned at each site, with use of a random-number generator, to follow either the low-carbohydrate diet or the conventional diet. Subjects in both groups were instructed to take a daily multivitamin supplement and met with a registered dietitian for 15 to 30 minutes at 3, 6, and 12 months to review dietary issues.

Low-Carbohydrate Diet

The 33 subjects who were assigned to the low-carbohydrate, high-protein, high-fat diet met individually with a registered dietitian before beginning the program to review the central features of the diet (available as Supplementary Appendix 1 with the full text of this article at http://www.nejm.org), which involves limiting carbohydrate intake without restricting consumption of fat and protein. For the first two weeks, carbohydrate intake is limited

Table 1. Base-Line Characteristics of the Subjects.*

Characteristic	Low-Carbohydrate Diet (N=33)	Conventional Diet (N=30)
Sex (no. of subjects)		
Male	12	8
Female	21	22
Race or ethnic group (no. of subjects)†		
White	26	22
Black	4	8
Hispanic	3	0
Age (yr)	44.0±9.4	44.2±7.0
Body-mass index‡	33.9±3.8	34.4±3.1
Weight (kg)	98.7±19.5	98.3±16.4
Systolic blood pressure (mm Hg)	120.5±11.0	123.3±14.1
Diastolic blood pressure (mm Hg)	74.6±8.5	77.6±10.8
Triglycerides (mg/dl)	131.1±113.8	122.6±82.6
Cholesterol (mg/dl)		
Total	200.5±33.5	193.7±32.1
Low-density lipoprotein	129.5±30.0	119.8±30.0
High-density lipoprotein	46.8±11.2	49.4±12.5
Area under the curve		
Glucose (mg/dl/2 hr)	15,649.7±2956.3	15,540.2±2623.8
Insulin (μU/ml/2 hr)	8776.7±5072.5	10,025.7±5845.5
Insulin sensitivity§	0.35±0.05	0.34±0.04

* Plus–minus values are means ±SD. There were no significant differences between the two groups. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. To convert values for cholesterol to millimoles per liter, multiply by 0.02586.
† The race or ethnic group was assigned by the subjects themselves.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Insulin sensitivity was calculated according to the quantitative insulin-sensitivity check index.[16]

Table 2. Percent Changes in Weight, Blood Pressure, Serum Lipoprotein Concentrations, and Oral Glucose Tolerance in an Analysis in Which Base-Line Values Were Carried Forward in the Case of Missing Data.*

Variable	Low-Carbohydrate Diet (N=33)	Conventional Diet (N=30)	P Value†
	percent change		
Weight			
Mo 3	−6.8±5.0‡	−2.7±3.7‡	0.001
Mo 6	−7.0±6.5‡	−3.2±5.6‡	0.02
Mo 12	−4.4±6.7‡	−2.5±6.3‡	0.26
Systolic blood pressure			
Mo 3	−2.6±11.2	−0.6±11.9	0.59
Mo 6	−2.3±11.7	1.0±12.2	0.28
Mo 12	−1.0±9.4	1.7±11.8	0.43
Diastolic blood pressure			
Mo 3	−3.0±13.4	−3.5±10.3‡	0.84
Mo 6	−4.0±12.7‡	−2.9±14.2	0.84
Mo 12	−3.7±12.4‡	−3.8±13.2	0.84
Triglycerides			
Mo 3	−18.7±25.7‡	1.1±34.6	0.01
Mo 6	15.0±29.4‡	−7.6±19.3‡	0.13
Mo 12	−17.0±23.0‡	0.7±37.7	0.04
Total cholesterol			
Mo 3	1.7±15.0	−5.4±10.1‡	0.03
Mo 6	2.4±9.3	−2.4±9.5	0.06
Mo 12	0.1±9.8	−2.9±8.0	0.27
Low-density lipoprotein cholesterol			
Mo 3	5.4±19.2	−7.4±16.6‡	0.007
Mo 6	2.7±12.8	−1.5±15.8	0.34
Mo 12	0.31±16.6	−3.1±12.0	0.52
High-density lipoprotein cholesterol			
Mo 3	9.6±19.1‡	1.4±16.1	0.04
Mo 6	14.7±20.5‡	2.5±12.0	0.007
Mo 12	11.0±19.4‡	1.6±11.1	0.04
Area under the glucose curve			
Mo 3	6.7±20.7	1.6±16.6	0.27
Mo 6	1.0±15.9	−0.8±12.2	0.80
Mo 12	3.2±16.2	1.2±10.1	0.80
Area under the insulin curve			
Mo 3	−14.1±27.6‡	−11.2±40.5‡	0.48
Mo 6	−14.7±25.7‡	−5.1±35.8	0.19
Mo 12	−11.2±24.7‡	−8.2±28.4‡	0.60
Insulin sensitivity§			
Mo 3	6.7±11.6‡	4.1±10.7	0.37
Mo 6	5.8±12.0‡	5.2±10.3‡	0.79
Mo 12	2.9±9.5	2.9±9.5	0.92

* Plus–minus values are means ±SD.
† P values are for the differences between the two groups.
‡ P<0.05 for the difference from base line within the group.
§ Insulin sensitivity was calculated according to the quantitative insulin-sensitivity check index.[16]

to 20 g per day and is then gradually increased until a stable and desired weight is achieved. Each subject was given a copy of *Dr. Atkins' New Diet Revolution*,[10] which details the Atkins diet program. Subjects were instructed to read the book and follow the diet as described.

Conventional Diet

The 30 subjects who were assigned to the conventional diet also met with a registered dietitian before beginning the program to review the components of a high-carbohydrate, low-fat, low-calorie diet (1200 to 1500 kcal per day for women and 1500 to 1800 kcal per day for men, with approximately 60 percent of calories from carbohydrate, 25 percent from fat, and 15 percent from protein) and to receive instructions about calorie counting. Subjects were given a copy of *The LEARN Program for Weight Management*,[17] which provides 16 lessons covering various aspects of weight control. The nutritional information in the manual was consistent with the dietary recommendations provided by the study dietitian and with the Department of Agriculture Food Guide Pyramid.[18] Subjects were instructed to read the manual and follow the program as described.

OUTCOMES

Body weight was measured with the use of calibrated scales (Detecto 6800, Cardinal) while the subjects were wearing light clothing and no shoes at base line and at weeks 2, 4, 8, 12, 16, 20, 26, 34, 42, and 52. Blood pressure and urinary ketones were also assessed at base line and at weeks 2, 4, 8, 12, 16, 20, 26, 34, 42, and 52. Blood samples were obtained after subjects fasted overnight at base line and at 3, 6, and 12 months to determine serum lipoprotein concentrations. An oral glucose-tolerance test was performed at base line and at 3, 6, and 12 months. After subjects fasted overnight, blood samples were obtained for the measurement of plasma glucose and insulin concentrations before and 30, 60, 90, and 120 minutes after the oral administration of a 75-g glucose load. In addition, insulin sensitivity, based on fasting plasma glucose and insulin concentrations, was assessed with the use of quantitative insulin-sensitivity check index[16]: 1÷[(log fasting serum insulin level, in microunits per milliliter)+(log fasting glucose level, in milligrams per deciliter)].

ANALYSES OF SAMPLES

Serum total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride concentrations

were assayed according to procedures recommended by the Centers for Disease Control and Prevention and the National Heart, Lung, and Blood Institute.[19] The low-density lipoprotein (LDL) cholesterol concentration was calculated according to the Friedewald formula[20] in all but one subject, who had a triglyceride concentration greater than 400 mg per deciliter (4.52 mmol per liter). Plasma insulin was measured by radioimmunoassay, and plasma glucose by a glucose oxidase autoanalyzer (Yellow Springs Instruments). The area under the curve (AUC) for the plasma glucose concentration and for the insulin concentration was calculated.[21] Urinary ketone concentrations were measured with dipsticks (Ketostix 2880, Bayer) and characterized dichotomously as negative (0 mg per deciliter) or positive (5 to 100 mg per deciliter).

STATISTICAL ANALYSIS

Analysis of variance revealed no effects of the research site on weight loss or attrition at 3, 6, or 12 months, so the data on all the subjects were analyzed together. A t-test for independent samples was used to assess differences in base-line variables between the groups. Two sets of analyses were conducted. The primary analysis was a repeated-measures analysis of variance in which the base-line value was carried forward in the case of missing data. In a secondary analysis, an analysis of covariance (in which initial weights were covariates) was used to examine changes in weight from base line to the end of the study, for those who completed the study, or at the time of the last follow-up visit, for those who did not complete the study. A chi-square analysis was performed to determine differences between groups in categorical variables, and correlations with categorical variables were assessed with Spearman's rho coefficient. Triglyceride values were not normally distributed, so the log-transformed values were analyzed. Results are presented as percent changes to facilitate clinical interpretation, although all analyses involved absolute values and were conducted with the use of SPSS software (version 11.0).[22]

RESULTS

WEIGHT

In the analysis in which base-line values were carried forward in the case of missing values, the group on the low-carbohydrate diet had lost significantly more weight than the group on the conventional diet at 3 months (P=0.001) and 6 months (P=0.02), but the difference in weight loss was not statistically significant at 12 months (P=0.26) (Table 2 and Fig. 1A).

ATTRITION

A total of 49 subjects completed 3 months of the study (28 on the low-carbohydrate diet and 21 on the conventional diet), 42 subjects completed 6 months (24 on the low-carbohydrate diet and 18 on the conventional diet), and 37 subjects completed 12 months (20 on the low-carbohydrate diet and 17 on the conventional diet). The percentage of subjects who had dropped out of the study at 3, 6, and 12 months was higher in the group following the conventional diet (30, 40, and 43 percent, respectively) than in the group following the low-carbohydrate diet (15, 27, and 39 percent, respectively), but these differences were not statistically significant. Overall, 59 percent of subjects completed the study, and 88 percent of those who completed the

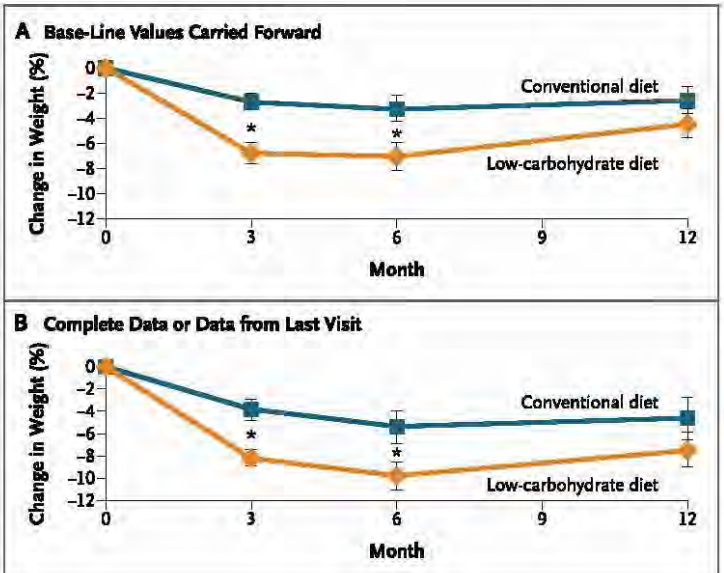

Figure 1. Mean (±SE) Percent Change in Weight among Subjects on the Low-Carbohydrate Diet and Those on the Conventional (Low-Calorie, High-Carbohydrate) Diet, According to an Analysis in Which Base-Line Values Were Carried Forward in the Case of Missing Values (Panel A) or an Analysis That Included Data on Subjects Who Completed the Study and Data Obtained at the Time of the Last Follow-up Visit for Those Who Did Not Complete the Study (Panel B).

In Panel B, the low-carbohydrate group had 28 subjects at 3 months, 24 subjects at 6 months, and 20 subjects at 12 months and the conventional-diet group had 21 subjects at 3 months, 18 subjects at 6 months, and 17 subjects at 12 months. Asterisks indicate a significant difference (P<0.05) between the groups.

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Table 3. Percent Changes in Weight, Blood Pressure, Serum Lipoproteins, and Oral Glucose Tolerance in an Analysis That Included Data on Subjects Who Completed the Study and Data Obtained at the Time of the Last Follow-up Visit for Those Who Did Not Complete the Study.*

Variable	Low-Carbohydrate Diet	Conventional Diet	P Value†
	percent change		
Weight			
Mo 3	−8.1±4.4‡	−3.8±3.9‡	0.002
Mo 6	−9.7±5.7‡	−5.3±6.4‡	0.03
Mo 12	−7.3±7.3‡	−4.5±7.9‡	0.27
Systolic blood pressure			
Mo 3	−3.1±12.1	−0.8±14.3	0.69
Mo 6	−3.2±12.7	1.6±15.9	0.36
Mo 12	−1.6±12.2	2.9±15.8	0.44
Diastolic blood pressure			
Mo 3	−3.5±14.5	−5.1±12.1‡	0.65
Mo 6	−5.5±14.7‡	−4.9±18.3	0.95
Mo 12	−6.1±15.6‡	−6.7±17.2	0.76
Triglycerides			
Mo 3	−22.0±26.6‡	1.7±42.8	0.03
Mo 6	−20.6±32.8‡	−13.3±24.3‡	0.27
Mo 12	−28.1±23.6‡	1.4±52.5	0.04
Total cholesterol			
Mo 3	2.0±16.3	−8.2±11.5‡	0.02
Mo 6	3.3±10.9	−4.2±12.5	0.06
Mo 12	0.2±12.7	−5.5±10.4	0.23
Low-density lipoprotein cholesterol			
Mo 3	6.2±20.4	−11.1±19.4‡	0.005
Mo 6	3.6±14.8	−2.7±21.1	0.35
Mo 12	0.5±21.2	−5.8±16.1	0.47
High-density lipoprotein cholesterol			
Mo 3	11.4±20.3‡	2.1±19.8	0.07
Mo 6	20.2±21.7‡	4.4±15.8	0.02
Mo 12	18.2±22.4‡	3.1±15.2	0.04
Area under the glucose curve			
Mo 3	7.9±22.3	2.3±19.9	0.33
Mo 6	1.4±18.7	−1.4±16.5	0.76
Mo 12	5.3±20.8	2.4±14.4	0.87
Area under the insulin curve			
Mo 3	−16.7±29.3‡	−16.0±48.0‡	0.23
Mo 6	−20.2±28.4‡	−9.0±47.8	0.37
Mo 12	−18.4±29.8‡	−16.5±39.1‡	0.34
Insulin sensitivity§			
Mo 3	7.9±12.3‡	5.9±12.4	0.56
Mo 6	8.0±13.4‡	8.7±12.1‡	0.94
Mo 12	4.8±12.0	5.4±12.7	0.98

* Plus–minus values are means ±SD. The low-carbohydrate group had 28 subjects at 3 months, 24 subjects at 6 months, and 20 subjects at 12 months. The conventional-diet group had 21 subjects at 3 months, 18 subjects at 6 months, and 17 subjects at 12 months.
† P values are for the differences between the two groups.
‡ P<0.05 for the difference from base line within the group.
§ Insulin sensitivity was calculated according to the quantitative insulin-sensitivity check index.[16]

six-month assessment completed the full study. When the analysis included data on subjects who completed the study and data obtained at the time of the last follow-up visit for those who did not complete the study, the pattern of weight loss was similar to that obtained when the base-line values were carried forward in the case of missing data. Subjects on the low-carbohydrate diet lost significantly more weight than the subjects on the conventional diet at 3 months (P=0.002) and 6 months (P=0.03), but the difference in weight loss was not statistically significant at 12 months (P=0.27) (Table 3 and Fig. 1B).

URINARY KETONES

During the first three months, the percentage of patients who tested positive for urinary ketones was significantly greater in the group on the low-carbohydrate diet than in the group on the conventional diet (Fig. 2), but there were no significant differences between the groups after three months. There was no significant relation between weight loss and ketosis at any time during the study.

BLOOD PRESSURE

Systolic blood pressure did not change significantly in either group during the study (Tables 2 and 3). Diastolic pressure decreased in both groups, but there were no significant differences between groups.

ORAL GLUCOSE-TOLERANCE TEST

The area under the glucose curve did not change significantly in either group throughout the study. The area under the insulin curve decreased in both groups, but there were no significant differences between groups (Tables 2 and 3). There were no significant differences between groups in insulin sensitivity (assessed by the quantitative insulin-sensitivity check index[16]) throughout the study period. Both groups had significant increases in insulin sensitivity at six months, but the values were not significantly different from base line at one year (Tables 2 and 3).

SERUM LIPOPROTEINS

The effects of the diets on serum lipoproteins are shown in Tables 2 and 3 and Figure 3. There were no significant differences between groups in the total or LDL cholesterol concentration, except at month 3, when values were significantly lower in the group on the conventional diet than in the group on the low-carbohydrate diet. In contrast, the rela-

tive increase in HDL cholesterol concentrations and the relative decrease in triglyceride concentrations were greater in the group on the low-carbohydrate diet than in the group on the conventional diet throughout most of the study. The results of the analyses that included data on subjects who completed the study and data obtained at the time of the last follow-up visit for those who did not complete the study (Table 3) were nearly identical to the analyses in which base-line values were carried forward in the case of missing data (Table 2) with respect to blood pressure, insulin sensitivity, and serum lipoproteins.

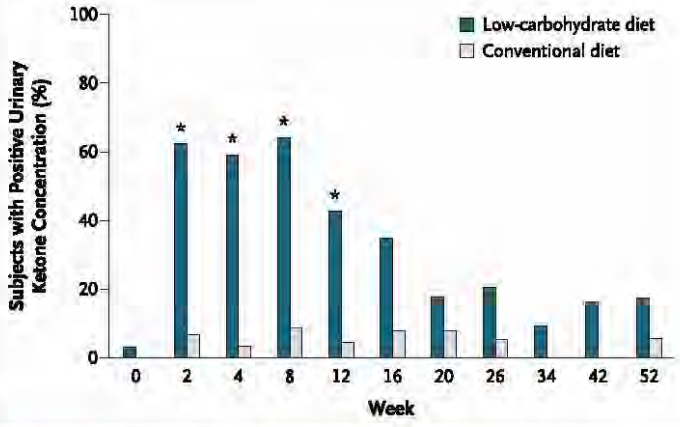

Figure 2. Percentage of Subjects with a Positive Urinary Ketone Concentration, According to Whether They Were on the Low-Carbohydrate Diet or the Conventional (Low-Calorie, High-Carbohydrate) Diet.

A positive urinary ketone concentration was defined as 5 to 100 mg per deciliter. Asterisks indicate a significant difference ($P<0.003$) between the groups.

DISCUSSION

The results of this multicenter, randomized, controlled trial demonstrate that the low-carbohydrate, high-protein, high-fat Atkins diet produces greater weight loss (an absolute difference of approximately 4 percent) than a conventional high-carbohydrate, low-fat diet for up to six months, but that the differences do not persist at one year. The magnitude of weight loss at six months in the low-carbohydrate group approximates that achieved by standard behavioral[23] and pharmacologic[24] treatments. These weight losses are particularly noteworthy because the diet was implemented in a self-help format and subjects had little contact with health professionals. The lack of a statistically significant difference between the groups at one year is most likely due to greater weight regain in the low-carbohydrate group and the small sample size. These data suggest that long-term adherence to the low-carbohydrate Atkins diet may be difficult.

The difference in weight loss between the two groups in the first six months demonstrates an overall greater energy deficit in the low-carbohydrate group, despite unrestricted protein and fat intake in this group and instructions to restrict energy intake in the conventional-diet group. When the energy content of an energy-deficit diet is stable, macronutrient composition does not influence weight loss.[25-28] The mechanism responsible for the decreased energy intake induced by a low-carbohydrate diet with unrestricted protein and fat intake is not known but may be related to the monotony or simplicity of the diet, alterations in plasma or central satiety factors, or other factors that affect appetite and dietary adherence. Our data suggest that ketosis was unlikely to be responsible for the increased weight loss with the low-carbohydrate diet, since we did not find any relation between the presence of urinary ketones and weight loss. Furthermore, urinary ketones were not present in most subjects on either diet after the first six months.

Although subjects with diabetes were excluded from our study, many — if not most — of our subjects, because of their obesity, were probably insulin-resistant with respect to glucose metabolism.[29] Treatment with either diet was associated with an improvement in insulin sensitivity as determined by an oral glucose-tolerance test; progressively less insulin was secreted to maintain the same blood glucose concentrations. These data do not demonstrate an effect of macronutrient composition, independent of weight loss, on insulin sensitivity in obese subjects without diabetes. However, the results of these metabolic studies should be interpreted with caution, given the study's relatively small sample size and the one-year duration. Additional studies in which more precise measures of insulin sensitivity are used are needed to evaluate this issue more carefully.

An important health concern of consuming unrestricted amounts of saturated fat is the potential to increase the LDL cholesterol concentration, which is an established risk factor for coronary heart disease. In fact, at three months, the LDL cholesterol concentration tended to increase in the subjects on the low-carbohydrate diet but decreased in the subjects on the conventional diet, so the difference be-

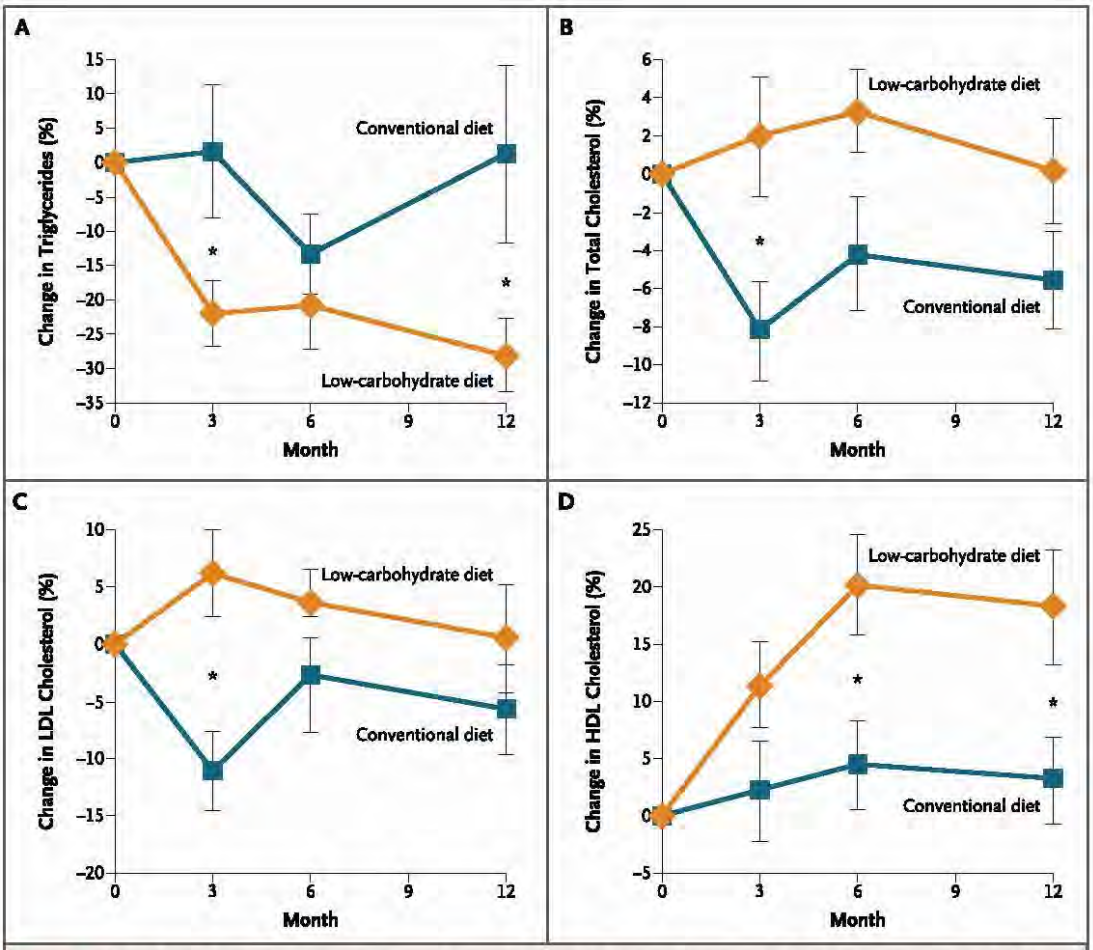

Figure 3. Mean (±SE) Percent Change in Serum Concentrations of Triglycerides (Panel A), Total Cholesterol (Panel B), Low-Density Lipoprotein (LDL) Cholesterol (Panel C), and High-Density Lipoprotein (HDL) Cholesterol (Panel D) among Subjects on the Low-Carbohydrate Diet and Those on the Conventional (Low-Calorie, High-Carbohydrate) Diet.

Data were obtained at the end of the study for subjects who completed the study and at the time of the last follow-up visit for those who did not complete the study. The low-carbohydrate group had 28 subjects at 3 months, 24 subjects at 6 months, and 20 subjects at 12 months. The conventional-diet group had 21 subjects at 3 months, 18 subjects at 6 months, and 17 subjects at 12 months. Asterisks indicate a significant difference ($P<0.05$) between the groups.

tween groups was significant. Over the long term, however, the LDL cholesterol concentration among subjects on the low-carbohydrate diet was similar to base-line values, and the changes in LDL cholesterol concentrations did not differ significantly between the groups. These data suggest that the increased weight loss associated with the low-carbohydrate diet may offset the adverse effect of saturated fat intake on serum LDL cholesterol concentrations. Nonetheless, weight loss with the low-carbohydrate diet was not associated with the decreases in LDL cholesterol usually observed with moderate weight loss.[4,30]

In contrast, the low-carbohydrate diet was associated with greater decreases in serum triglycerides and greater increases in HDL cholesterol than was the conventional diet, and the levels of both are also important risk factors for coronary heart disease.[31-33] The magnitude of these changes approximates that obtained with pharmacologic treatments, such as derivatives of fibric acid and niacin.[31] Although part of this benefit may be due to the greater weight loss with the low-carbohydrate diet, the changes are greater than those expected from a moderate weight loss alone.[30] Therefore, it is likely that the macronutrient composition of the diet

contributed to the improvement in the HDL cholesterol–triglyceride axis. High-carbohydrate, low-fat diets decrease HDL cholesterol concentrations and increase serum triglyceride concentrations,[34-37] whereas low-carbohydrate, high-fat diets decrease triglyceride concentrations[16,27,37] and increase HDL cholesterol concentrations.[15] Moreover, replacing dietary polyunsaturated or monounsaturated fat with carbohydrate is associated with an increased risk of coronary heart disease, as predicted by changes in triglyceride and HDL cholesterol concentrations.[38]

The overall effect of the low-carbohydrate diet in comparison with a conventional diet on the risk of coronary heart disease in our subjects is uncertain. As compared with the conventional diet, the low-carbohydrate diet was associated with a greater improvement in some risk factors for coronary heart disease (serum triglycerides and serum HDL cholesterol), but not others (blood pressure, insulin sensitivity, and serum LDL cholesterol). Moreover, the clinical significance of the favorable changes in the HDL cholesterol–triglyceride axis in the setting of a high fat intake is not clear. Additional, long-term studies are needed to determine whether increased serum HDL cholesterol concentrations and decreased serum triglyceride concentrations have the same effect on cardiovascular outcomes when one is consuming a diet high in saturated fat. It is also possible that the large amount of saturated fats and small amounts of fruits, vegetables, and fiber consumed during the low-carbohydrate diet can independently increase the risk of coronary heart disease.[39,40] Therefore, at the present time, there is not enough information to determine whether the beneficial effects of the Atkins diet outweigh its potential adverse effects on the risk of coronary heart disease in obese persons.

Our study has several limitations. The self-help nature of treatment, which is consistent with the way in which the low-carbohydrate diet is typically used, probably contributed to the attrition rate of 41 percent. This high rate of attrition underscores the difficulty of long-term compliance with either diet, when diet therapy is given with minimal supervision. More comprehensive behavioral treatment (e.g., weekly group meetings or self-monitoring) would probably have decreased attrition, increased adherence, and made possible a comparison with clinic-based treatments for obesity.[23] Our study was focused on weight and specific risk factors for coronary heart disease. We did not evaluate the effect of the low-carbohydrate diet on other important clinical end points, such as renal function, bone health, cardiovascular function, and exercise tolerance. Finally, our findings should not be generalized to overweight subjects or to obese subjects with serious obesity-related diseases, such as diabetes and hypercholesterolemia. Additional studies are needed in these populations to evaluate the safety and efficacy of low-carbohydrate, high-protein, high-fat diets.

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Will All Americans Become Overweight or Obese? Estimating the Progression and Cost of the US Obesity Epidemic

Youfa Wang[1], May A. Beydoun[1], Lan Liang[2], Benjamin Caballero[1] and Shiriki K. Kumanyika[3]

We projected future prevalence and BMI distribution based on national survey data (National Health and Nutrition Examination Study) collected between 1970s and 2004. Future obesity-related health-care costs for adults were estimated using projected prevalence, Census population projections, and published national estimates of per capita excess health-care costs of obesity/overweight. The objective was to illustrate potential burden of obesity prevalence and health-care costs of obesity and overweight in the United States that would occur if current trends continue. Overweight and obesity prevalence have increased steadily among all US population groups, but with notable differences between groups in annual increase rates. The increase (percentage points) in obesity and overweight in adults was faster than in children (0.77 vs. 0.46–0.49), and in women than in men (0.91 vs. 0.65). If these trends continue, by 2030, 86.3% adults will be overweight or obese; and 51.1%, obese. Black women (96.9%) and Mexican-American men (91.1%) would be the most affected. By 2048, all American adults would become overweight or obese, while black women will reach that state by 2034. In children, the prevalence of overweight (BMI ≥ 95th percentile, 30%) will nearly double by 2030. Total health-care costs attributable to obesity/overweight would double every decade to 860.7–956.9 billion US dollars by 2030, accounting for 16–18% of total US health-care costs. We continue to move away from the Healthy People 2010 objectives. Timely, dramatic, and effective development and implementation of corrective programs/policies are needed to avoid the otherwise inevitable health and societal consequences implied by our projections.

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INTRODUCTION

Obesity has become a public health crisis in the United States. Nationally representative survey data show that the prevalence has steadily increased over the past three decades although there are large disparities between population groups and continuing changes in the associated patterns (1–3). Current evidence suggests that the prevalence is likely to remain on the rise (1,4,5), and it will not be possible to meet the objectives set for Healthy People 2010 of reducing obesity prevalence in adults to 15% and in children to 5% (6). Obesity has many health, social, psychological, and economic consequences for the individuals being affected and for the society (7). The current US generation may have a shorter life expectancy than their parents if this obesity epidemic cannot be controlled (8). The economic impact is especially evident in health-care costs (9–13). A recent study estimated that medical expenditures attributed to overweight and obesity accounted for 9.1% of total US medical expenditures in 1998 and might have reached 78.5 billion US dollars (10). Expenditures will continue to rise particularly due to the increases in obesity prevalence and in the cost of related health care (11).

This study aims to provide a thorough analysis to illustrate potential future trends in obesity and the related health-care costs were current trends to continue, based on nationally representative survey data collected over the past three decades, to characterize the need for national polices and programs. Such information will help the United States and perhaps other policy makers, health professionals, and the general public to be better prepared to face the related challenges, and motivate the development of public health and clinical programs to address the obesity epidemic in order to avoid the many adverse health and social consequences that will otherwise ensue.

METHODS AND PROCEDURES

Overview

Our projection analyses were based on prevalence data from the National Health and Nutrition Examination Study (NHANES)

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collected between the 1970s and 2004 (ref. 14). Compared with other available data sources, the NHANES provides high quality, directly measured height and weight data from nationally representative samples, and the data are comparable over time (1). Our projections of obesity-related health-care costs are mainly based on recently published studies using national health-care expenditure data.

Key outcome variables

Overweight and obesity. For practical purposes and among both children and adults, BMI (weight (kg)/height (m)^2) is widely used nowadays to assess obesity (15–18). In adults, the BMI (kg/m^2) cut-off points for overweight and obese are set at 25 and 30, respectively (17,19). In children and adolescents, "Overweight" is defined as BMI (kg/m^2) ≥ the sex–age-specific 95th BMI percentile, and "at risk for overweight" as 85th ≤ BMI <95th percentile (20–22). In children and adolescents, we focused on overweight because national estimates of the prevalence of "at risk for overweight" have not been made available for all waves of NHANES.

Health-care costs attributable to obesity and overweight. Medical costs associated with overweight and obesity may involve direct and indirect costs (13). Direct medical costs may include preventive, diagnostic, and treatment services related to obesity. Indirect costs relate to morbidity and mortality. Morbidity costs are defined as the value of income lost from decreased productivity, restricted activity, absenteeism, and bed days. Mortality costs are the value of future income lost by premature death. Note that our projections only provide estimates of the overall direct medical costs. We chose not to estimate the indirect costs because of the larger uncertainty and the need for more data. In addition, we focused on adults in our cost projections because of the absence of published estimates on health-care costs attributable to obesity for children or adolescents.

Main original databases used for projections

NHANES. The NHANES comprises a series of cross-sectional, nationally representative examination surveys conducted since the 1970s including NHANES I (1971–1974), II (1976–1980), and III (1988–1994). Beginning in 1999, NHANES became a continuous survey. Data on weight and height are collected through direct physical examination in a mobile examination center (14). Most recently, the NHANES data collected in 2003–2004 were made available. Previous analyses show little increase in the prevalence of obesity and overweight between NHANES I and II, but prevalence has been steadily increasing since NHANES II (1,3,23).

Medical Expenditure Panel Survey and National Health Expenditure Accounts. Recently published studies that estimate obesity-related health-care costs using the Medical Expenditure Panel Survey (MEPS) data (10,11) provide a base for our projections of future health-care costs attributable to overweight and obesity. The MEPS is a set of large-scale nationwide surveys of families and individuals, their medical providers (primarily doctors, hospitals, and pharmacies), and employers across the United States, which is designed to support studies of health-care use and expenditures (24,25). The survey began in 1996 and collects data on the specific health services that Americans use, how frequently they use them, the cost of these services, and how they are paid for, as well as data on the cost, scope, and health insurance coverage. National Health Expenditure Account (NHEA) provides aggregate measures of health-care expenditures in the United States by type of service delivered (hospital care, physician services, nursing home care, etc.) and source of funding for those services (private health insurance, Medicare, Medicaid, out-of-pocket spending, etc.). The Office of the Actuary in the Centers for Medicare and Medicaid Services annually produces projections of health-care spending for categories within the NHEA for the next decade (26).

Statistical analysis

Projection of future overweight and obesity trends. We estimated the average annual increase in the prevalence of overweight and obesity and predicted the future prevalence among US adults and children assuming the trends would be similar to those of the past three decades. Most of the past prevalence estimates based on NHANES data used in our analysis were based on previously published estimates, all of which were based on analyses done with consideration of survey design effects and sampling weights (1,3,23). Additional estimates were obtained only when necessary (e.g., prevalence and shift in BMI distributions) and were also calculated taking design effects and sample weights into account. For example, such analyses were conducted using the survey-related commends in STATA Release 9.0 (Stata, College Station, TX), and the relevant strata, primary sampling units, and sampling weight variables were used. We fit linear regression models with the prevalence as the dependent variable and the survey time as the predictors for different sociodemographic groups. The β coefficients indicate the average annual increases in the prevalence. The models fit the data well in each sociodemographic stratum, and explained 60–100% (i.e., R^2) of the variance in the prevalence. The majority (~90%) of the models had an $R^2 > 0.90$. Based on the findings, we then projected the future situation for the years of 2010, 2020, and 2030 as well as when the prevalence would reach the landmark levels (e.g., 80 and 100%). In addition, we calculated prediction intervals based on the s.e. of the predicted prevalence (27).

Further, based on previously observed BMI distribution shifts between 1976 and 2004 we predicted future BMI distributions among American adults aged ≥20 and then projected the mean BMI and prevalence based on these projected BMI distributions. We created weighted percentiles for each wave and estimated mean BMI within each percentile. Subsequently, the cumulative relative frequency (proportion) was compared between waves and the yearly shift in mean BMI for each percentile was estimated using ordinary least squares linear regression models with survey mid-period as the predictor for mean BMI in each percentile. This yearly shift was then applied to the NHANES 1999–2004 population to project future BMI distributions.

Projection of obesity-related health-care costs. We make two sets of projections based on our projected prevalence and two recently published estimates of per capita excess health-care costs attributable to obesity and overweight among US adults (10,11). Thorpe *et al.* used the MEPS and found that in 2001 the average health-care costs for the obese group was $1,069 higher than for the normal weight group, and for the overweight (25 ≤ BMI < 30) group, was higher by $340 (refs. 10,11). Finkelstein *et al.* estimated that the annual excess health-care costs attributable to obesity were $732 per person in 1998, and $247 for overweight (10). We estimated per capita excess health-care costs due to obesity and overweight for each year from 2000 to 2030, assuming that the excess costs grow at the same rate as per capita personal health-care costs in the NHEA, which have been projected to 2016 (ref. 28). We applied the average annual growth rate of per capita personal health costs between 2005 and 2016, 6.0%, to the rest of the study period.

To calculate total health-care costs attributable to obesity and overweight for all US adults, we applied our projected prevalence to the population projection provided by the Census Bureau. We also expressed these costs as a percentage of the total personal health-care costs in the NHEA, and as a percentage of total health-care costs estimate from MEPS. Total personal health-care costs in the NHEA are projected to grow at 6.9% from 2016 to 2030, the same as the annualized growth rate from 2005 to 2016 projected. Total health-care expenditures from MEPS are available for 1996–2004. We assume that these estimates grow at the same rate as the NHEA personal health-care costs. Note that primarily because of coverage differences (e.g., sample population included) that MEPS estimates of total health-care expenditures are lower than those of the NHEA (29). The projected costs were also converted to 2,000 dollars assuming a 3% annualized increase in the gross domestic product deflator.

Table 1 Average annual increase in prevalence of obesity and overweight among US adults and children and future projections based on NHANES 1976–1980 to 2003–2004

Age	Gender	Ethnicity	Current (1999–2004)	Average annual increase (percentage points) (OLS)			Prevalence projections: prevalence (%) and projection interval		
				Rate (β)	s.e.	R^2	2010	2020	2030
Adults, ≥20 years	Men and women	All	66.3	0.772	0.044	0.99	70.8 (68.4–73.1)	78.5 (75.6–81.4)	86.3 (82.9–89.8)
Overweight and obesity (BMI ≥ 25 kg/m²)	Men	All	67.0	0.653	0.022	0.99	73.5 (72.3–74.7)	80.1 (78.5–81.7)	86.6 (84.6–98.6)
	Women	All	62.0	0.911*	0.153	0.97	69.0 (60.9–77.0)	78.1 (67.5–88.7)	87.2 (73.9–100.0)
	Men	Non-Hispanic white	67.5	0.654	0.017	0.99	74.7 (73.7–75.7)	81.3 (80.1–82.5)	87.8 (86.2–89.4)
		Non-Hispanic black	60.1	0.419*	0.083	0.96	64.3 (73.7–75.7)	68.5 (80.1–82.5)	72.7 (86.2–89.4)
		Mexican American	74.4	0.595	0.003	1	79.3 (79.1–79.5)	85.2 (85.0–85.4)	91.1 (90.9–91.3)
	Women	Non-Hispanic white	57.5	0.856*	0.152	0.97	65.2 (57.2–73.2)	73.7 (63.3–84.1)	82.3 (69.2–95.4)
		Non-Hispanic black	78.0	0.694*	0.180	0.94	83.0 (73.4–92.6)	90.0 (77.5–100)	96.9 (81.2–100)
		Mexican American	71.8	0.481*	0.094	0.96	77.1 (72.0–82.2)	81.9 (75.4–88.4)	86.7 (78.5–94.9)
Obesity (BMI ≥ 30 kg/m²)	Men and women	All	32.2	0.682	0.031	0.99	37.4 (35.6–39.2)	44.2 (42.2–46.2)	51.1 (48.5–53.6)
	Men	All	27.7	0.685*	0.064	0.98	33.9 (30.6–37.2)	40.7 (36.4–45.0)	47.6 (42.1–53.1)
	Women	All	34.0	0.778*	0.070	0.98	42.5 (38.8–46.2)	50.3 (45.4–55.0)	58.0 (51.9–64.1)
	Men	Non-Hispanic white	31.1	0.727	0.037	0.99	34.3 (32.3–36.3)	41.5 (38.9–44.0)	48.8 (45.7–51.9)
		Non-Hispanic black	34.0	0.636	0.141	0.87	36.4 (28.7–44.0)	42.7 (33.1–52.3)	49.1 (37.3–60.9)
		Mexican American	31.6	0.575	0.075	0.97	33.3 (29.2–37.4)	39.0 (33.9–43.3)	44.8 (38.5–51.1)
	Women	Non-Hispanic white	30.2	0.616	0.055	0.98	35.6 (32.7–38.5)	41.7 (38.0–45.4)	47.9 (43.4–52.4)
		Non-Hispanic black	53.9	0.878	0.107	0.97	58.1 (52.2–64.0)	66.9 (59.6–74.1)	75.6 (66.6–84.6)
		Mexican American	42.3	0.569	0.084	0.96	44.4 (39.9–48.9)	50.1 (44.4–57.8)	55.8 (48.7–62.8)
Children, 6–11 years	Boys and girls	All	18.8	0.462	0.051	0.97	20.4 (17.6–23.1)	25.0 (21.5–28.5)	29.7 (25.4–34.0)
Overweight (BMI ≥ 95th percentile)[a]	Boys	All	19.9	0.492	0.052	0.97	20.8 (12.0–29.6)	25.7 (22.2–29.2)	30.7 (26.4–35.0)
	Girls	All	17.6	0.406	0.041	0.97	19.8 (17.4–22.1)	23.8 (21.0–26.5)	27.9 (24.6–31.2)
	Boys	Non-Hispanic white	18.5	0.4	0.100	0.84	19.7 (14.2–25.2)	23.7 (17.0–30.4)	27.7 (19.5–35.9)
		Non-Hispanic black	17.5	0.441	0.029	0.99	21.4 (19.8–23.0)	25.8 (23.8–27.8)	30.2 (27.8–32.5)
		Mexican American	25.3	0.548	0.098	0.91	30.2 (24.7–35.7)	35.7 (29.2–42.2)	41.1 (33.0–49.1)
	Girls	Non-Hispanic white	16.9	0.403	0.073	0.91	17.0 (12.9–21.1)	21.1 (16.2–26.0)	25.1 (19.0–31.2)
		Non-Hispanic black	26.5	0.564	0.056	0.97	28.2 (25.1–31.3)	33.9 (30.2–37.6)	39.5 (34.8–44.2)
		Mexican American	19.4	0.314*	0.142	0.62	20.2 (12.4–28.0)	23.4 (14.0–32.8)	26.5 (14.7–38.3)

Table 1 Continued on next page

Table 1 Average annual increase in prevalence of obesity and overweight among US adults and children and future projections based on NHANES 1976–1980 to 2003–2004 (Continued)

Age	Gender	Ethnicity	Current (1999–2004)	Average annual increase (percentage points) (OLS)			Prevalence projections: prevalence (%) and projection interval		
				Rate (β)	s.e.	R^2	2010	2020	2030
Adolescents, 12–19 years	Boys and girls	All	17.4	0.492	0.016	0.99	21.1 (19.7–22.5)	26.0 (24.4–27.6)	31.0 (29.2–32.8)
	Boys	All	18.3	0.528	0.018	0.99	21.1 (19.3–22.8)	26.4 (24.4–28.4)	31.6 (29.0–34.1)
Overweight (BMI ≥ 95th percentile)[a]	Girls	All	16.4	0.449	0.022	0.98	18.8 (17.2–20.4)	23.3 (21.5–25.0)	27.8 (25.4–30.1)
	Boys	Non-Hispanic white	19.1	0.526	0.108	0.88	20.0 (13.9–26.1)	25.2 (17.9–32.4)	30.5 (21.5–39.5)
		Non-Hispanic black	18.5	0.537	0.129	0.85	22.1 (14.8–29.3)	27.4 (18.8–36.0)	32.8 (22.2–43.4)
		Mexican American	18.3	0.589	0.226	0.69	25.3 (12.7–37.8)	31.2 (16.1–46.3)	37.1 (18.5–55.7)
	Girls	Non-Hispanic white	15.4	0.391	0.058	0.94	16.9 (13.7–20.0)	20.8 (16.9–24.7)	24.7 (20.0–29.4)
		Non-Hispanic black	25.4	0.581	0.096	0.92	29.5 (24.2–35.8)	35.3 (28.8–41.8)	41.1 (33.3–48.9)
		Mexican American	14.1	0.36*	0.154	0.64	20.4 (11.8–29.0)	24.0 (13.6–34.4)	27.6 (14.8–40.3)

Ordinary least squares (OLS) linear regression models included prevalence as a function of time as the independent variable. The β coefficients can be interpreted as the annual change in prevalence. Note that time periods for each National Health and Nutrition Examination Study (NHANES) survey (1976–2004) were represented by the mid-point of the survey period. For Mexican American, only NHANES data collected between 1988 and 2004 were adequate and used in our projection. The projections were conducted assuming no population distribution changes regarding age, sex, and ethnicity after 2004. Prediction intervals were estimated after estimating the predicted projection s.e. for each projection year. 95% confidence intervals were estimated as predicted prevalence ± 1.96 × s.e.
[a]Based on the 2000 CDC Growth Charts.
*$P > 0.05$ for null hypothesis that $\beta = 0$; all the others $P < 0.05$.

All analyses were conducted using STATA Release 9.0. We have considered other projection methods, but felt the presented approaches are appropriate and provide straightforward and interpretable results. Our linear models had excellent fit as shown by the high R^2 values. Our projected results based on year-specific prevalence (linear models) and those based on BMI distribution are consistent. Even though prediction intervals were estimated in our study, literal prediction of the future scenario in the United States would be affected by many possible uncertainties including policy-, environmental-, and behavioral changes that would require many more assumptions and more complex models than were applied here. Rather we aimed to show in a relatively straightforward manner what the future would be if the trends observed in the past continue.

RESULTS

Projected prevalence of overweight and obesity from 2010 to 2030

On average, the prevalence of overweight and obesity has increased steadily among all US population groups over the past two to three decades ($P < 0.05$), but some noticeable differences exist in the average annual increase (percentage point) across sex-, age-, and ethnic groups (Table 1 and Figure 1). In general, US adults saw a faster increase in obesity than the increase in overweight in children and adolescents (0.68 vs. 0.46 and 0.49, respectively); women had a faster increase than men (0.91 vs. 0.65 for combined prevalence of overweight and obesity). Girls had a slower increase in overweight than boys (0.41 vs. 0.49 in children and 0.45 vs. 0.53 in adolescents). White men and women had the highest increase rate in the combined prevalence, compared with African Americans and Mexican Americans (MAs), within gender. Regarding obesity, African-American women had the highest prevalence and rate

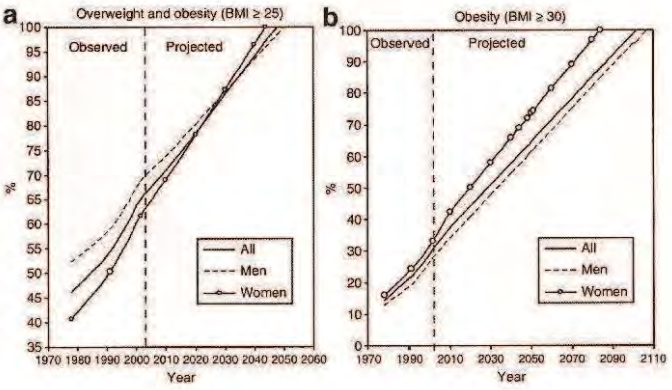

Figure 1 Prevalence of obesity and overweight among US adults: Observed during 1976–2004 and projected. The projected prevalence presented here are those based on our linear regression models.

of increase overall; and in men, the prevalence was similar, but white men had the highest increase rate. The patterns in children and adolescents were complex.

Our projection models show that by the year 2030, ~90% (86.3%) of all American adults would become overweight or obese and 51.1% of them would be obese. Black women (combined prevalence 96.9%) and MA men (91.1%) would be the groups most affected. In children and adolescents, prevalence of overweight would increase 1.6-fold (to ~30%) by 2030. MA young boys and black adolescent girls would have the highest prevalence (both 41.1%), a level that would be 10 percentage points higher than the national average. Further, the prevalence

Table 2 Future projections:[a] time when the prevalence of overweight or obesity among US adults will reach 80, 85, 90, and 100% and prevalence of overweight (BMI ≥ 95th percentile[b]) among US children will reach 30, 40, and 50%

	Gender	Ethnicity	Year when the prevalence will reach 80%	90%	100%
US adults					
Overweight and obesity (BMI ≥ 25 kg/m²)	All	All	2022	2035	2048
	Men	All	2020	2035	2051
	Women	All	2022	2033	2044
	Men	Non-Hispanic white	2018	2033	2049
		Non-Hispanic black	2047	2071	2095
		Mexican American	2011	2028	2045
	Women	Non-Hispanic white	2027	2039	2051
		Non-Hispanic black	2006	2020	2034
		Mexican American	2016	2037	2058
Obesity (BMI ≥ 30 kg/m²)	All	All	2072	2087	2102
	Men	All	2077	2092	2107
	Women	All	2058	2071	2084
	Men	Non-Hispanic white	2073	2087	2100
		Non-Hispanic black	2079	2094	2110
		Mexican American	2091	2109	2126
	Women	Non-Hispanic white	2082	2098	2115
		Non-Hispanic black	2035	2046	2058
		Mexican American	2073	2090	2108
US children and adolescents			**Year when the prevalence will reach 30%**	**40%**	**50%**
Children, 6–11 years	All	All	2031	2052	2074
Overweight[b]	Boys	All	2029	2049	2069
	Girls	All	2035	2060	2084
	Boys	Non-Hispanic white	2036	2061	2086
		Non-Hispanic black	2029	2052	2075
		Mexican American	2010	2028	2046
	Girls	Non-Hispanic white	2042	2067	2092
		Non-Hispanic black	2013	2031	2049
		Mexican American	2041	2073	2105
Adolescents, 12–19 years	All	All	2028	2048	2069
	Boys	All	2027	2046	2065
	Girls	All	2035	2057	2080
Overweight[b]	Boys	Non-Hispanic white	2029	2048	2067
		Non-Hispanic black	2025	2043	2062
		Mexican American	2018	2035	2052
	Girls	Non-Hispanic white	2043	2069	2095
		Non-Hispanic black	2011	2028	2045
		Mexican American	2037	2064	2092

[a]The projections were made using linear regression models based on National Health and Nutrition Examination Study data collected between 1974 and 2004, and assumed no population distribution changes regarding age, sex, and ethnicity after 2004. [b]Based on the 95th BMI percentiles in the 2000 CDC Growth Chart.

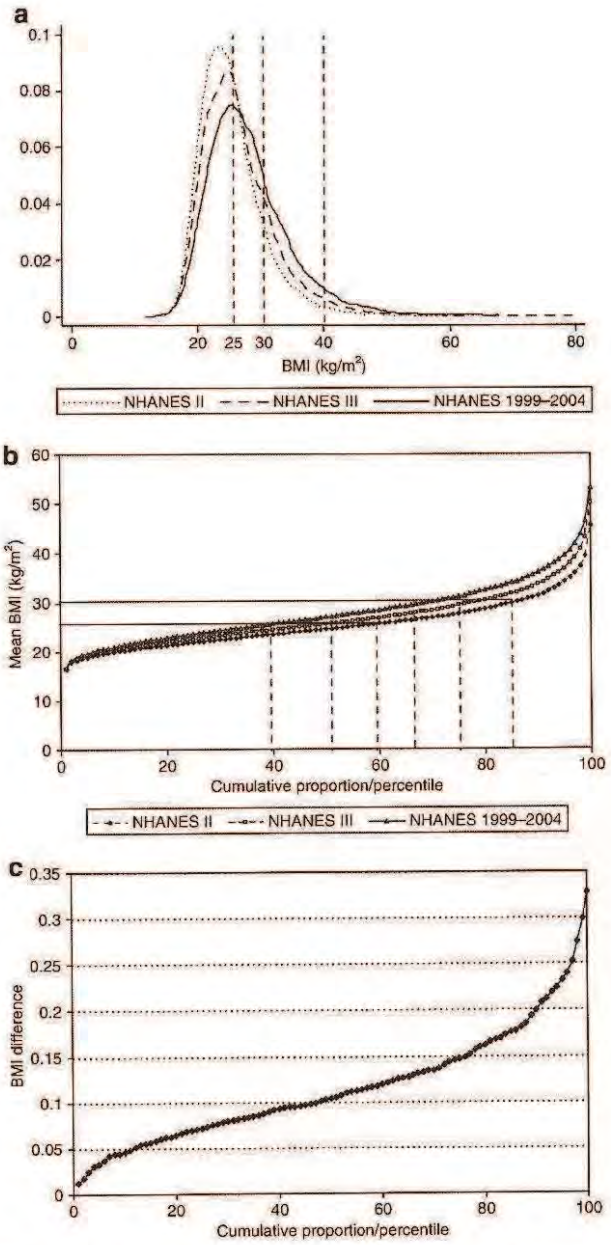

Figure 2 Shifts in BMI distribution among American adults between 1976 and 2004: NHANES II (1976–1980), III (1988–1994), and 1999–2004. (**a**) Kernel density plot of BMI. (**b**) Cumulative proportion distribution of BMI. (**c**) Mean BMI difference within percentile, *m–d*: ordinary least squares (OLS) estimate of average yearly shift.

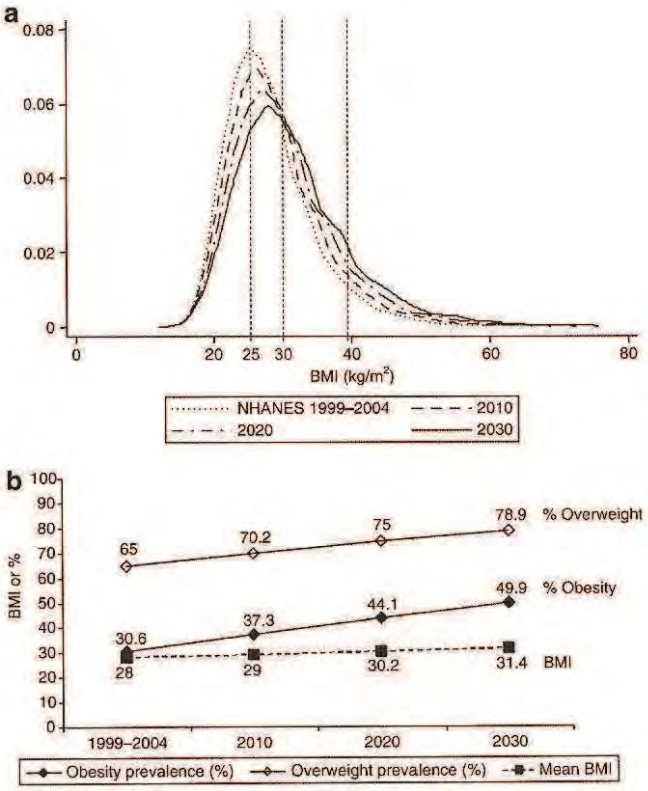

Figure 3 Current BMI distribution and projected distributions for the years of 2010, 2020, and 2030. (**a**) BMI Kernel density plots. (**b**) Mean BMI, obesity, and overweight prevalence.

Table 3 Projected direct health-care costs, in billions of dollars, attributable to overweight and obesity for US adults: 2000–2030

	Overweight and obesity (BMI ≥ 25 kg/m²)				Obesity (BMI ≥ 30 kg/m²)			
	Billions ($)	Billions of $2,000	% NHEA	% MEPS	Billions ($)	Billions of $2,000	% NHEA	% MEPS
Projection A[a]								
2000	81.5	$81.5	7.1	13.0	60.9	$60.9	5.3	9.7
2010	194.3	$151.1	8.4	13.5	151.3	$117.7	6.5	10.5
2020	437.6	$276.0	9.7	15.6	351.1	$221.4	7.8	12.5
2030	956.9	$507.5	10.9	17.6	784.8	$416.2	9.0	14.4
Projection B[b]								
2000	72.2	$72.2	6.3	11.5	53.2	$53.2	4.7	8.5
2010	175.2	$136.3	7.6	12.2	114.6	$104.7	5.8	9.4
2020	394.0	$248.5	8.8	14.1	312.3	$197.0	6.9	11.2
2030	860.7	$456.4	9.8	15.8	698.3	$370.3	8.0	12.8

MEPS, Medical Expenditure Panel Survey; NHEA, National Health Expenditure Account.
[a]Projection based on per capita excess health-care costs attributable to obesity and overweight estimated by Thorpe *et al.* (11). [b]Projection based on per capita excess health-care costs attributable to obesity and overweight estimated by Finkelstein *et al.* (10).

in MA adolescents will increase by twofold and among African-American teens, by 1.8-fold, the largest increases.

Furthermore, our findings from comparing BMI distributions between NHANES II (1976–1980) and 1999–2004 suggest a great BMI increase in the upper part of the distribution. Note that a previous study has examined the shift up to NHANES III (1988–1994) (ref. 30). This is clearly shown in the increasing area under the upper tail, the widening of the BMI mean differences in the upper percentiles and an upward sloping *m–d* plot (Figure 2). Assuming these trends will persist, we projected the future BMI distributions. Based on these projections, mean BMI will increase linearly from 27.9 in 1999–2004 to 31.2 in 2030; and by 2030, 78.9% of American adults will be overweight or obese, while 49.9% will be obese (Figure 3). In general, these results are consistent with our linear regression model–based projections.

Time course to arrive at 100% prevalence

In ~15 years, by the year 2022, 80% of American adults would be overweight or obese; and the prevalence would reach 100% in ~40 years (by the year 2048) (Table 2 and Figure 1). For black women, the time course to reach 100% prevalence is <30 years (by 2034). Half of US children and adolescents overall will become overweight around the year 2070, but this level will be reached among black girls and MA boys by 2050.

The projected obesity-related direct health-care costs

Total health-care costs attributable to obesity and overweight will be more than doubled every decade (Table 3). By 2030, health-care costs attributable to obesity and overweight could range from $860 to $956 billion, which would account for 15.8–17.6% of total health-care costs, or for 1 in every 6 dollars spent on health care. Because of the assumptions we made and the limitations of the available data, these figures are likely an underestimation of the true impact.

DISCUSSION

Our analyses, based on nationally representative data collected over the past three decades and the assumptions of similar future increase rate and health costs as observed in the past, clearly show an alarming picture of the future obesity epidemic and related challenges. Our projections show that if the trends continue, in only 15 years 80% of all American adults will be overweight or obese. The potential for all adults to become overweight or obese is a reality, especially for subgroups such as black women where the current prevalence is already 78%. At the current rate of increase it will take <30 years for all black women to become overweight or obese. Our projections also indicate that the direct health-care costs attributable to obesity and overweight will be more than doubled every decade. By 2030, costs could range from 860.7 to 956.9 billion US dollars, accounting for 1 in every 6 dollars spent on health care. This is likely to be a gross underestimate, as we assumed that the obesity-related per capita health-care costs grow at the same rate as the per capita total health-care costs, when some evidence suggests that the gap between per capital spending between obese and normal weight individuals in fact is growing significantly larger over time (11). For example, possible future changes such as earlier onset of obesity and complications in younger adults and availability of more costly health-care services may substantially increase related health-care costs.

Although some may question the assumption that the observed trends in the past 30 years will continue and some ongoing and future policy and program changes may affect the future trends, based on the current literature, there are few signs that the increase will slow down. It is possible that the increase may slow down when the future prevalence reaches a high level or due to emerging effective interventions. On the other hand, there are continuing changes in the society (e.g., contextual environmental factors) and people's lifestyles that may put a growing proportion of the population at increased risk for obesity. In fact, the increase observed among black women over the past two decades and the recent catch up of prevalence in white women provide some evidence to support this concern. The potential role of social norms in promoting obesity development was suggested by an analysis of weight gain within social networks (31). Increasing proportions of the population who are obese may result in changes in attitudes about what constitutes a healthy body weight. The environmental and behavioral forces fueling the obesity epidemic are unlikely to be modified overnight, and even effective prevention programs may take years to show a significant impact.

A clear implication of our findings is that the national objectives specified in Healthy People 2010 related to obesity cannot be met, except for the limitations of this study (e.g., the assumptions made). These objectives need be reassessed and reframed to be more realistic and to provide the motivation for a paced but deliberate effort to stabilize and then reverse the trends of obesity increase. A growing body of research aiming at a better understanding of the underlying causes of the growing obesity epidemic suggests that complex factors operating interactively at multiple levels (e.g., individual, community/school, society, and international) are important contributors to this national public health crisis (7,32–34). For a problem as pervasive and serious as the obesity epidemic we have observed at present and projected for the future in the United States, it is likely that broad, comprehensive approaches are needed to address it.

As articulated by the World Health Organization for the global situation (35) and by the Institute of Medicine with respect to childhood obesity in the United States (36), dramatic and effective population-based programs and related policies need to be developed and implemented to address the epidemic. But until recently, there were few truly multifactorial prevention initiatives, the focus being instead on changing individual behaviors. More recently, there has been increasing recognition of the major role that the "obesogenic" environment plays in perpetuating the epidemic (37–39). What is needed now are creative initiatives to actually effect environmental changes, and this will require a strong and sustained collaboration among the public and private sectors, educators, food producers, urban planners, transportation experts, parents, and the general public. The nation's health-care system should be prepared to face the rising burden of obesity-related health consequences, by providing more relevant training to medical and health-care professionals and developing the needed infrastructures.

Our study has certain limitations. As noted previously, our projections are based on a number of assumptions, some of which are simplified scenarios. Future policy-, environmental- and behavioral changes may prove these assumptions wrong. Future obesity rates may not proceed linearly as the epidemic continues, while our projections essentially assume that the environment will continue to worsen at past rates. Other potentially relevant factors include a segment of the population that may be genetically protected from obesity or who may maintain a lower risk of developing obesity through persistent healthy lifestyle behaviors. The forces of the US obesity epidemic may not affect such individuals. In addition, our projected obesity-related medical costs were probably underestimates considering that more obese people will be severely obese in the future; thus, health-care costs per obese person will be higher. Future obesity-related health costs will also be higher due to the

availability of more expensive related services. Careful exploration of these complex factors was beyond the scope of this study and the information provided by currently available data.

It is our hope that the predicted grim future of the obesity epidemic will not turn into the actual scenario in the United States or any other countries. Projections for population subgroups that already have a prevalence of 80%, e.g., black women, suggest that it is indeed possible for the hypothetical levels estimated here to become a reality. Although some individuals may be less prone, genetically, to gain excess weight, we might indeed be approaching environmental and behavioral conditions such that few are exempt.

We hope that the results presented here will provide evidence of the severity of the obesity epidemic, of its impacts on the society, the lessons that other countries can learn from the United States, and ultimately, of the recognition that we, collectively, are the only ones who can prove these projections wrong. Hence, we offer these analyses to pose the questions—what obesity prevalence will be acceptable going forward? What goals will we set, and how will we attain these goals?

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DISCLOSURE

The authors declared no conflict of interest.

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Systematic Review with Meta-analysis

Very-low-carbohydrate ketogenic diet *v.* low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials

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Abstract

The role of very-low-carbohydrate ketogenic diets (VLCKD) in the long-term management of obesity is not well established. The present meta-analysis aimed to investigate whether individuals assigned to a VLCKD (i.e. a diet with no more than 50 g carbohydrates/d) achieve better long-term body weight and cardiovascular risk factor management when compared with individuals assigned to a conventional low-fat diet (LFD; i.e. a restricted-energy diet with less than 30 % of energy from fat). Through August 2012, MEDLINE, CENTRAL, ScienceDirect, Scopus, LILACS, SciELO, ClinicalTrials.gov and grey literature databases were searched, using no date or language restrictions, for randomised controlled trials that assigned adults to a VLCKD or a LFD, with 12 months or more of follow-up. The primary outcome was body weight. The secondary outcomes were TAG, HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), systolic and diastolic blood pressure, glucose, insulin, HbA_{1c} and C-reactive protein levels. A total of thirteen studies met the inclusion/exclusion criteria. In the overall analysis, ve outcomes revealed signicant results. Individuals assigned to a VLCKD showed decreased body weight (weighted mean difference −091 (95 % CI −165, −017) kg, 1415 patients), TAG (weighted mean difference −018 (95 % CI −027, −008) mmol/l, 1258 patients) and diastolic blood pressure (weighted mean difference −143 (95 % CI −249, −037) mmHg, 1298 patients) while increased HDL-C (weighted mean difference 009 (95 % CI 006, 012) mmol/l, 1257 patients) and LDL-C (weighted mean difference 012 (95 % CI 004, 02) mmol/l, 1255 patients). Individuals assigned to a VLCKD achieve a greater weight loss than those assigned to a LFD in the long term; hence, a VLCKD may be an alternative tool against obesity.

Key words:Cardiovascular risk factors: Low-carbohydrate diets: Meta-analysis: Obesity: Weight loss

Obesity continues to be a major worldwide health problem, despite the efforts of the medical community. At least 28 million adults die from obesity-related causes each year, and 65 % of the worldwide population lives in countries where obesity causes more deaths than underweight[1]. Although it is a difcult task, intensive lifestyle interventions can achieve weight loss that is sustained over the long term, as shown by the ndings of a recent large clinical trial [2].

Diet is a cornerstone of any lifestyle intervention programme. The dietary plan that restricts energy and fat is the most common strategy, and based on it, several other dietary strategies have been proposed[3–5]. The very-low-carbohydrate ketogenic diet (VLCKD) differs from these approaches. According to Accurso*et al.* [6], in the early phases of this therapy, individuals must have approximately 50 g carbohydrates/d or 10 % of energy from a nominal 8400 kJ (approximately 2000 kcal) diet, unlike low-carbohydrate diets, which may have up to 130 g carbohydrates/d or 26 % of energy from a nominal diet. A major concern regarding the prescription of the VLCKD is the adherence of the individuals assigned to it, since it promotes important lifestyle changes[7].

Given the importance of dietary counselling in weight loss, it is useful to investigate the effectiveness of different dietary therapies. A recent large randomised clinical trial, which assigned individuals to diets ranging from 35 to 65 % of dietary carbohydrate content, showed that, at this level of carbohydrate intake, there is no difference in weight loss between interventions[8]. Nonetheless, evidence suggests

Abbreviations: DBP, diastolic blood pressure; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; LFD, low-fat diet; SBP, systolic blood pressure; VLCKD, very-low-carbohydrate ketogenic diet; WMD, weighted mean differences.

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that greater dietary carbohydrate restrictions lead to greater weight loss[9]. Indeed, previous meta-analyses have shown that carbohydrate-restricted diets promote greater weight loss than conventional energy-restricted low-fat diets (LFD)[10,11]. However, these analyses did not exclusively focus on VLCKD studies[10], or included mostly trials with 6 months of follow-up[11]; hence, these analyses do not guarantee the long-term effectiveness of the VLCKD.

A recent meta-analysis by Santos *et al.*[12] reported that low-carbohydrate diets lead to signicantly favourable changes in body weight and major cardiovascular risk factors. Nevertheless, this analysis was based only on the individuals who had adopted a low-carbohydrate diet, comparing nal values against baseline values. Although it was an important investigation, the question of whether an abrupt change to an individuals lifestyle, such as the adoption of a VLCKD, leads to relevant long-term clinical improvements remains unanswered.

Thus, the present meta-analysis evaluated randomised controlled trials to determine whether overweight and obese individuals assigned to a VLCKD achieve greater weight loss and manage cardiovascular risk factors more effectively than those assigned to a LFD over the long term (dened as 12 months or more post-intervention).

Methods

The present meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement[13]. The protocol was previously published in the PROSPERO database (http://www.crd.york.ac.uk/PROSPERO), under registration no. CRD42012002408.

Search strategy

The following databases were searched until August 2012: MEDLINE, CENTRAL, ScienceDirect, Scopus, LILACS, SciELO and ClinicalTrials.gov. In addition, the following grey literature databases were searched: OpenGrey.eu, DissOnline.de, NYAM.org and ClinicalEvidence.com. There was no manual search of the included articles, and no specialists in the eld were contacted to avoid the risk of citation bias[14]. The search strategy included terms related to the intervention (VLCKD), the primary outcome (weight loss) and the secondary outcomes (cardiovascular risk factors), as well as related terms designed to improve the sensitivity of a search for randomised controlled trials[15]. The search was not restricted to any particular years of publication or languages. The complete search strategy is shown in the Supplementary material (available online).

Eligibility criteria

Only randomised controlled trials that met the following criteria were included: (1) the study participants were individuals older than 18 years old who were assigned to a LFD (i.e. a restricted-energy diet with less than 30 % of energy from fat) or to a VLCKD (i.e. a diet with no more than 50 g carbohydrates/d or 10 % of daily energy from carbohydrates); (2) the follow-up period was 12 months or more; (3) the participants had a mean BMI greater than 275 kg/m^2. The third criterion allowed the inclusion of studies of populations who are already at high risk beyond this BMI threshold[16].

The present analysis aimed to evaluate the differences in the outcomes of the prescribed diets, without addressing individual adherence to the diets. There were no restrictions based on sex, race or co-morbidities. At a minimum, the studies must have assessed weight loss as an outcome and must have reported mean values or the differences between the mean values. The exclusion criteria were as follows: (1) studies with a concomitant pharmacological intervention and (2) duplicate publications of the included trials.

Data extraction

The titles and abstracts of the retrieved articles were evaluated independently by two investigators who were not blinded to the authors or the journal titles. The full-text versions of potentially eligible articles were retrieved for further evaluation.

The primary outcome sought in the studies was the mean change between the baseline body weight and the nal body weight (in kg), with the associated measure of dispersion. The secondary outcomes were the mean changes between the baseline and nal values (with the associated measures of dispersion) for TAG (in mg/dl (to convert to mmol/l, multiply by 00113)), HDL-cholesterol (HDL-C) and LDL-cholesterol (LDL-C) (in mg/dl (to convert to mmol/l, multiply by 00259)), fasting blood glucose (in mg/dl (to convert to mmol/l, multiply by 00555)), insulin (in mU/ml (to convert to pmol/l, multiply by 6945)), C-reactive protein (in mg/l (to convert to nmol/l, multiply by 9524)), HbA_{1c} (percentage), and systolic and diastolic blood pressure (SBP and DBP, respectively, in mmHg).

All the necessary information was extracted from the published articles, protocols and commentaries related to each study, and when necessary, the authors were contacted to obtain additional information. For the studies that had more than two experimental groups, the most suitable one was chosen. Any disagreements were resolved by consensus. A standard form for storing data was created based on the Cochrane Collaboration model[17].

Assessment of risk of bias

Risk of bias was evaluated according to the Cochrane Handbook recommendations[18], at the primary outcome level. The quality of the studies were assessed by two investigators independently in ve categories: adequate sequence generation; allocation concealment; blinding of the outcome assessors; handling of missing data (intention-to-treat or per-protocol analysis); selective outcome reporting. The nature of the trials required an open intervention with no blinding of the trial participants or the investigators.

Data analysis

The absolute changes for each outcome, reported as the differences between the nal and baseline mean values,

were analysed. The treatment effects across the trials were pooled, and weighted mean differences (WMD) for the outcome measures were calculated. The study weights were assigned by using the inverse variance method[19], and the calculations were performed using a random-effects model[20]. An α value of 005 was considered to be statistically significant. When it was not possible to retrieve adequate data, imputations were performed[21]. These imputations are shown in the Supplementary material (available online).

Statistical heterogeneity among the studies was tested using the Cochran Q test, and inconsistency was tested using the I^2 test. A Pvalue less than 010 was considered to be statistically significant. Whenever a result showed heterogeneity, it was explored in three different ways. First, each analysis was repeated, removing each study one at a time in order to assess whether a particular study explained the heterogeneity. Second, univariate meta-regressions were performed to analyse whether methodological covariates were inuencing the results[22]. The covariates included the risk of bias in the study, adequate nutritional counselling of the individuals (studies that included individual or group meetings with a dietitian at least bimonthly until the end of the follow-up period were considered as adequate), the use of an intention-to-treat analysis, the study follow-up length in months and the presence of co-morbidities in the inclusion criteria for the participants in each study. Thereafter, it was planned to perform a multivariate meta-regression including all covariates that had a Pvalue less than 010 in the univariate analysis. Finally, subgroup analyses were performed on studies that shared certain methodological features, including studies with a low risk of bias, studies using an intention-to-treat analysis and studies with 24 months of follow-up. Subgroup analyses were conducted regardless of heterogeneity.

Contour-enhanced funnel plots[23] were created and Eggers test[24] was performed to evaluate publication bias; Pvalues less than 010 were considered to be statistically significant. All analyses were conducted using Stata software 9.0 (StataCorp). Graphs were plotted using RevMan 5.4 (Cochrane Collaboration).

Results

Included studies

From 3123 potentially relevant records identied by searching the databases, twenty-ve full-text publications met the inclusion criteria and were retrieved for further assessment. From these, eleven were excluded after the full-text analysis, leaving fourteen full texts included in the qualitative and quantitative analysis (Table 1). The ow diagram illustrating the search and selection of studies is shown in Fig. 1. Reasons for exclusion are shown in the Supplementary material (available online).

From the fourteen full-text articles included, the report by Vetter *et al.*[25] had characteristics that were unexpected and not mentioned in the inclusion or exclusion criteria for the review. This report describes a body weight analysis of the individuals included in the study by Sternet *al.* [26], conducted 36 months after randomisation. Nevertheless, follow-up ceased after 12 months; thus, it was not possible to assess whether the individuals continued with the intervention in the period after follow-up, so the data from this full-text article were included in a sensitivity analysis.

In total, thirteen studies were included in the quantitative analysis, with a total of 1577 individuals randomised to a condition (787 to a LFD group and 790 to a VLCKD group). From these, six studies had more than two intervention groups, and it was determined by consensus which groups t best in the analysis. Intervention groups of all studies are shown in the Supplementary material (available online).

Assessment of risk of bias

The risk of bias in the studies at the primary outcome level is shown in Table 2. In the nal result, nine from the thirteen included studies were assessed as having a low risk of bias.

Of these nine studies, two did not report the sequence generation method used, while seven did not report using any measure to conceal the allocation. All the nine studies did not report blinding of the outcome assessors, but as all

Table 1. Characteristics of the included studies

Source	Duration (months)	Dietary counselling	Dropouts (*n*/*N*)	Females (%)	Country	Risk factor	Mean age (years)	Mean BMI (kg/m^2)	CHO intake/d (VLCKD)*
Brinkworth*et al.* [28]	12	Adequate	38/107	70	Australia	CV risk factor	50·6	33·6	36 g
Dansinger*et al.* [50]	12	Inadequate	41/80	47	USA	CV risk factor	47	35	190 g
Davis*et al.* [51]	12	Adequate	14/105	78	USA	T2D	53·5	35·9	33 %
Dyson*et al.* [52]	24	Inadequate	4/26	73	UK	T2D	52	35·1	Unreported
Foster*et al.* [53]	12	Inadequate	37/63	68	USA	None	44·9	34·1	Unreported
Foster*et al.* [27]	24	Adequate	113/307	68	USA	None	45·5	36·1	Unreported
Gardner*et al.* [30]	12	Inadequate	26/153	100	USA	None	42	32	34 %
Iqbal *et al.*[29]	24	Adequate	76/144	10	USA	T2D	60	37·4	47 %
Lim*et al.* [54]	15	Inadequate	25/60	80	Australia	CV risk factor	48·4	31·4	36 %
McAuley*et al.* [55]	12	Inadequate	15/63	100	NZ	None	45	36·1	33 %
Shai *et al.*[49]	24	Adequate	44/213	16	Israel	CV risk factor	51·5	30·7	40 %
Stern*et al.* [26]	12	Adequate	45/132	17	USA	None	53·5	42·9	120 g
Truby*et al.* [56]	12	Inadequate	98/116	72	UK	None	39·8	32	Unreported

CHO, carbohydrate; VLCKD, very-low-carbohydrate ketogenic diet; CV, cardiovascular; T2D, type 2 diabetes mellitus; NZ, New Zealand.
* Mean carbohydrate intake in the VLCKD group at the end of the follow-up, measured by dietary assessment, shown as g/d or percentage of energy from carbohydrates per d. Truby *et al.*[56] assessed only the body weight at 12 months.

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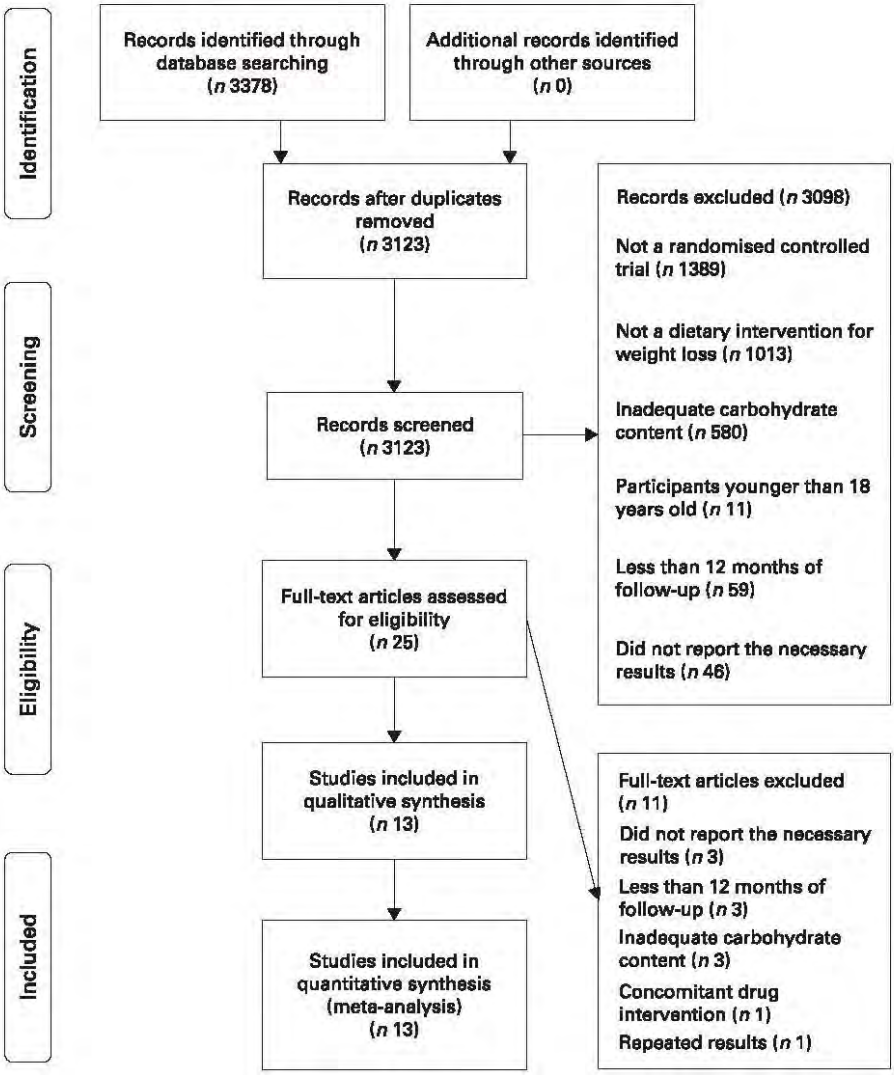

Fig. 1. Flow diagram of the study selection.

the outcomes are objective, it is unlikely that this domain affected the results of the trials. Regarding the handling of missing data, ve studies were categorised as having a high risk of bias because they utilised a per-protocol analysis. There was no evidence of selective outcome reporting.

Data analysis

Body weight. All the thirteen included studies (1415 patients) were assessed (Fig. 2(a)). The individuals assigned to a VLCKD achieved a signicantly greater weight loss compared with the individuals assigned to a LFD (WMD −091 (95% CI −165, −017) kg, P=002; I^2 = 0%, P=047). This result was consistent across all subgroup analyses, except for the subgroup of studies with 24 months of follow-up (data not shown). The substitution of the data from Stern *et al.*[26] for the data from Vetter*et al.* [25] changed the results (WMD −073 (95% CI −152, 006) kg, P=007; I^2 = 5%, P=039). There was no evidence of publication bias (P=034). The contour-enhanced funnel plots for body weight and all other outcomes are shown in the Supplementary material (available online).

TAG. In total, twelve studies (1258 patients) were assessed (Fig. 2(b)). The individuals assigned to a VLCKD showed a signicantly greater reduction in TAG than the individuals assigned to a LFD (WMD −018 (95% CI −027, −008) mmol/l, P<0001; I^2 =12%, P=033). This result was consistent across all subgroup analyses, except for the subgroup of studies with 24 months of follow-up (data not shown). Heterogeneity was reversed when the study by Foster *et al.*[27] was excluded, and also when the study by Stern*et al.* [26] was excluded, but there were no statistically signicant changes in the results. The evidence of publication bias (P=004) was also reversed with the exclusion of both aforementioned studies. The meta-regression analysis showed that the covariate study follow-up length affected the results signicantly (r^2 8719%, P=009; Table 3).

HDL-cholesterol. Overall, twelve studies (1257 patients) were assessed (Fig. 2(c)). The individuals assigned to a VLCKD achieved a signicantly greater increase in their

Table 2. Risk of bias of the included studies

Source	Sequence generation	Allocation concealment	Blinding	Missing data	Selective report	Overall
Brinkworth *et al.*[28]	Low	High	Unclear	Low	Low	High
Dansinger *et al.*[50]	Low	Low	Low	Low	Low	Low
Davis *et al.*[51]	Low	High	Unclear	Low	Low	High
Dyson *et al.*[52]	Low	Low	Low	High	Low	Low
Foster *et al.*[53]	Low	Unclear	Unclear	Low	Low	Low
Foster *et al.*[27]	Low	Unclear	Unclear	Low	Low	Low
Gardner *et al.*[30]	Low	Low	Low	Low	Low	Low
Iqbal *et al.*[29]	Low	Unclear	Unclear	Low	Low	Low
Lim *et al.*[54]	Unclear	Unclear	Unclear	High	Low	High
McAuley *et al.*[55]	Low	Low	Unclear	High	Low	Low
Shai *et al.*[49]	Low	Unclear	Low	Low	Low	Low
Stern *et al.*[26]	Low	Unclear	Unclear	Low	Low	Low
Truby *et al.*[56]	Low	Unclear	High	High	Low	High

HDL-C levels compared with the individuals assigned to a LFD (WMD 009 (95% CI 006, 012) mmol/l, $P<0001$; $I^2 = 9\%$, $P=036$). All the subgroups showed the same result (data not shown). The study by Brinkworth *et al.*[28] and the study by Iqbal *et al.*[29] were each individually responsible for the heterogeneity in the overall analysis, and the stepwise exclusion of both studies did not change the main result (data not shown). In the meta-regression analysis, only the covariate study follow-up length signicantly affected the results ($r^2 = 100\%$, $P=003$; Table 3). There was no evidence of publication bias ($P=053$).

LDL-cholesterol. A total of twelve studies (1255 patients) were assessed (Fig. 2(d)). The individuals assigned to a VLCKD achieved a signicantly greater increase in their LDL-C levels compared with the individuals assigned to a LFD (WMD 012 (95% CI 004, 02) mmol/l, $P=0002$; $I^2 = 0\%$, $P=07$). The subgroup of studies with 24 months of follow-up was the only subgroup that showed different results (data not shown). There was no evidence of publication bias ($P=042$).

Systolic and diastolic blood pressure. Overall, eleven studies (1298 patients) were included in the SBP (Fig. 3(A)) and DBP analyses (Fig. 3(B)). There were no differences in SBP between the groups (WMD in favour of the VLCKD −147 (95% CI −344, 050) mmHg, $P=014$; $I^2 = 33\%$, $P=013$), a result that held in the subgroup analyses. However, individuals assigned to a VLCKD had a signicantly greater reduction in DBP than the individuals assigned to a LFD (WMD −143 (95% CI −249, −037) mmHg, $P=0008$; $I^2 = 3\%$, $P=041$).

The sensitivity analysis for SBP showed that the study by Gardner *et al.*[30] was responsible for the heterogeneity, and its exclusion did not change the results (data not shown). The covariate adequate nutritional counselling signicantly affected the SBP results ($r^2 = 797\%$, $P=005$; Table 3). Due to the extremely low heterogeneity, neither a sensitivity analysis nor a meta-regression analysis was undertaken for DBP, and only the subgroup of studies with 24 months of follow-up showed different results (data not shown). There was no evidence of publication bias for SBP ($P=079$), but the DBP analysis showed statistically signicant publication bias ($P=004$), which was not reversed by the exclusion of any study.

Fasting blood glucose, insulin, HbA_{1c} and C-reactive protein. These analyses were performed in less than ten studies; thus, no sensitivity, subgroup, meta-regression and publication bias analyses were conducted. None of these analyses showed statistically signicant results. The forest plots for these analyses are shown in the Supplementary material (available online). For the fasting blood glucose analysis, eight studies (770 patients) were assessed (WMD in favour of the VLCKD −008 (95% CI −018, 002) mmol/l, $P=011$; $I^2 = 0\%$, $P=088$). For the insulin analysis, six studies (584 patients) were assessed (WMD in favour of the VLCKD −552 (95% CI −1362, 257) pmol/l, $P=018$; $I^2 = 26\%$, $P=024$). For the HbA_{1c} analysis, four studies (319 patients) were assessed (WMD in favour of the VLCKD −024 (95% CI −055, 006)%, $P=012$; $I^2 = 0\%$, $P=059$). Finally, for the C-reactive protein analysis, four studies (355 patients) were also assessed (WMD in favour of the VLCKD −185 (95% CI −666, 296) nmol/l, $P=045$; $I^2 = 0\%$, $P=055$).

Discussion

The present meta-analysis showed that individuals assigned to a VLCKD achieve greater reductions in body weight, TAG and DBP, but they also demonstrate a greater increase in LDL-C and HDL-C levels over a treatment follow-up period of 12 months or more, compared with individuals assigned to a LFD. Only the change in HDL-C levels retained statistical signicance in the subgroup analysis of studies with 24 months of follow-up; however, it is important to note that this analysis included only four studies. Low risk of bias was not unanimous, although this characteristic did not inuence any of the results, since potential bias was explored by conducting subgroup and meta-regression analyses. Also, studies that included individuals with co-morbidities were not sources of heterogeneity. Furthermore, only the TAG and the DBP analyses revealed evidence of publication bias.

With regard to the primary outcome, the present ndings are similar to the ndings of previous meta-analyses [10,11]. The supposed benecial effect of a VLCKD on body weight may be due to the modulation of resting energy expenditure.

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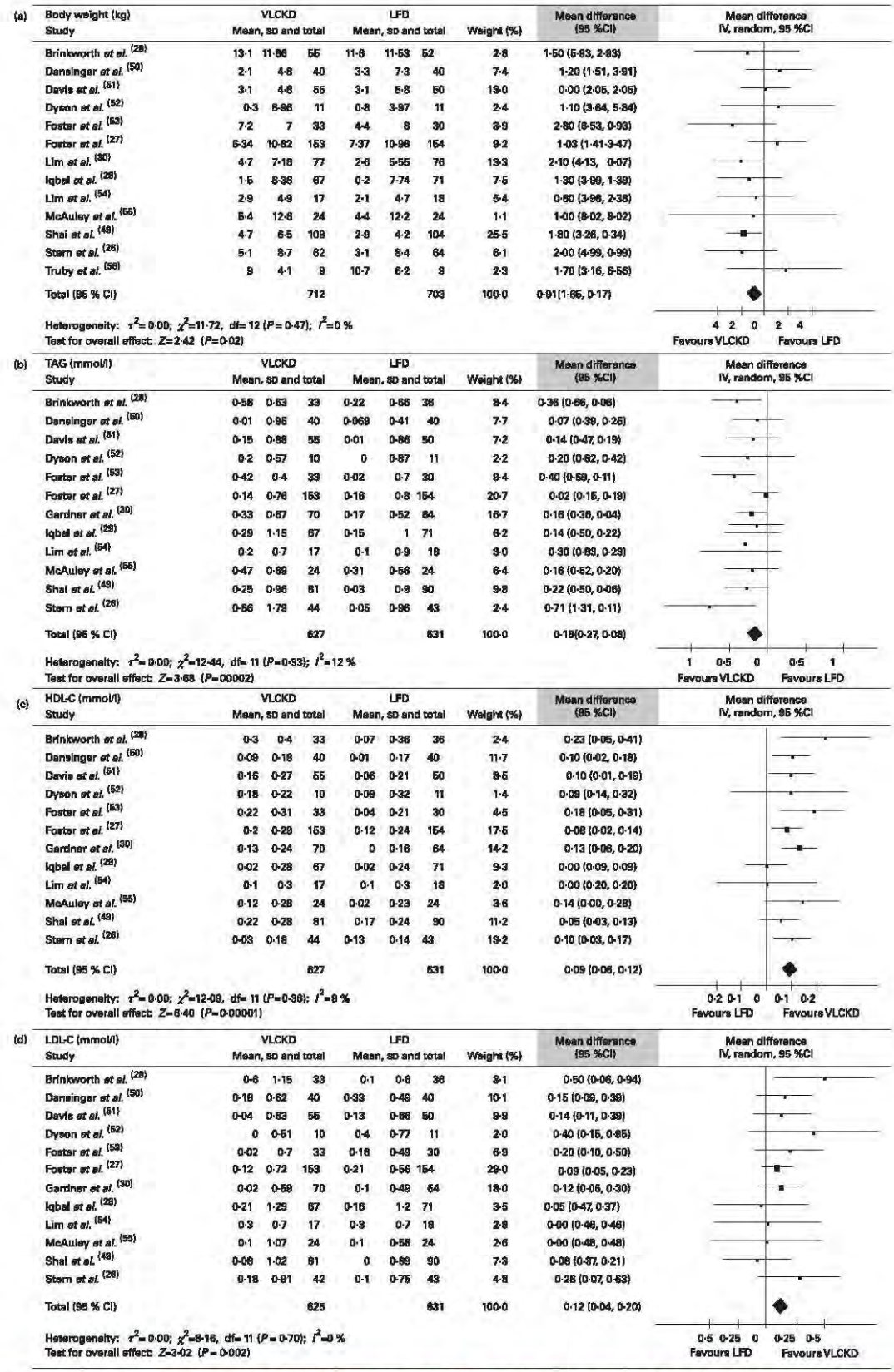

Fig. 2.Absolute changes in (a) body weight, (b) TAG, (c) HDL-cholesterol (HDL-C) and (d) LDL-cholesterol (LDL-C). VLCKD, very-low-carbohydrate ketogeni c diet; LFD, energy-restricted low-fat diet.

Table 3. Meta-regression analysis
(Coefficients and 95 % confidence intervals)

Covariates	Coefficient	95 % CI	Adj r^2 (%)	*P*
Adequate nutritional counselling				
TAG (mmol/l)	4·051	−17·008, 25·110	−9·67	0·677
HDL-C (mmol/l)	−1·645	−4·030, 0·740	100·00	0·155
Systolic blood pressure (mmHg)	3·582	−0·167, 7·333	79·79	0·059
Co-morbidities				
TAG (mmol/l)	−2·498	−23·740, 18·742	−17·52	0·799
HDL-C (mmol/l)	−1·542	−3·852, 0·768	100·00	0·168
Systolic blood pressure (mmHg)	2·309	−2·063, 6·682	28·18	0·263
Intention-to-treat analysis				
TAG (mmol/l)	13·173	−8·286, 34·632	34·23	0·201
HDL-C (mmol/l)	−0·406	−3·233, 2·421	−644·4	0·755
Systolic blood pressure (mmHg)	−0·946	−6·441, 4·548	−13·25	0·706
Length of the follow-up				
TAG (mmol/l)	1·259	−0·261, 2·781	87·19	0·095
HDL-C (mmol/l)	−0·208	−0·404, −0·013	100·00	0·039
Systolic blood pressure (mmHg)	0·094	−0·318, 0·506	−1·55	0·619
Low risk of bias				
TAG (mmol/l)	13·494	−7·867, 34·656	33·87	0·186
HDL-C (mmol/l)	0·117	−2·610, 2·845	−510·1	0·925
Systolic blood pressure (mmHg)	−1·821	−7·270, 3·627	−6·98	0·469

Adj r^2, adjusted r^2; HDL-C, HDL-cholesterol.

Under isoenergetic conditions, Ebbeling*et al.* [31] found that a carbohydrate-restricted diet is better than a LFD for retaining an individuals BMR. In addition, Westman *et al.*[32] hypothesised that a VLCKD reduces insulin levels, which would explain the satietogenic effects of this diet. This hypoinsulinaemic effect of the VLCKD was not evidenced in this analysis.

TAG decreased signicantly in individuals assigned to a VLCKD. The heterogeneity in the analysis and the evidence of publication bias were entirely attributable to the study by Foster *et al.*[27], which was the only study to present neutral results in this analysis. On the other hand, individuals assigned to a VLCKD showed signicantly increased levels of both LDL-C and HDL-C levels. As discussed by Volek*et al.* [33], the preservation of the circulating HDL-C and the hypotriacylglycerolaemic effect of a VLCKD might be explained by the reduction in the dieting individuals postprandial lipaemia. Conversely, the increase in LDL-C concentration associated with the VLCKD is an expected nding that is attributable to the increase in saturated fat intake. However, this nding warrants further investigation. Krauss *et al.*[34] showed that high fat intake, combined with carbohydrate restriction, raises the levels of larger-sized LDL-C, which are known to be less atherogenic than the small, dense LDL-C[35].

There was also evidence that individuals assigned to a VLCKD showed a signicantly greater reduction in DBP. Hession *et al.*[10] analysed ve studies and found that carbohydrate-restricted diets only inuenced SBP. Usually, hypertension is attributable to obesity and Na intake, but Appel *et al.*[36] showed that substituting carbohydrates for proteins and monounsaturated fats may decrease blood pressure beyond the decrease expected with Na restriction alone.

It is remarkable to note that although ve outcomes demonstrated statistical signicance, these ndings must be carefully interpreted regarding its clinical signicance [37]. For example, a typical 170 m-tall adult with a BMI of 30 kg/m^2 weighs 87 kg; hence, a weight loss of 091 kg, as observed here, would represent only 104 % of the initial body weight. However, large randomised clinical trials with long-term dietary interventions aiming weight loss showed that individuals under intensive lifestyle interventions lose about 48 kg [2,38]. Hence, the further reduction of 09 kg in the individuals assigned to a VLCKD would represent almost 20 % of the awaited weight loss achieved with long-term dietary interventions. Additionally, if we assume the cut-off points of the metabolic syndrome[39], similar percentages would be found regarding the other outcomes. The extra reduction of 143 mmHg in DBP achieved by individuals assigned to a VLCKD is similar to the reductions promoted by other dietary interventions, such as Mg supplementation[40] or consumption of avonol-rich products [41].

Undoubtedly, the present ndings demonstrate that a VLCKD has favourable effects on body weight and some cardiovascular risk factors, as stated by Santos*et al.* [12]; however, in the long term and when compared with conventional therapy, the differences appear to be of little clinical signicance, although statistically signicant. Healthcare professionals should weigh the advantages and disadvantages of recommending a VLCKD and consider their patients will power, since this therapy prominently alters an individuals daily habits.

The present meta-analysis has several limitations. First, it used aggregated data from the studies instead of individual patient data. Second, only blood risk factors were assessed, neglecting important pathological markers such as hepatic lipid inltration [42], endothelial function[43], general cardiovascular events[44] and renal function[45], which are important in assessing the safety of dietary therapies. Third, the adherence to the VLCKD in the included studies was low (Table 1). At the end of the follow-up period in most studies, carbohydrate intake was higher than the protocol allowed. However, in most cases, there was good adherence in the

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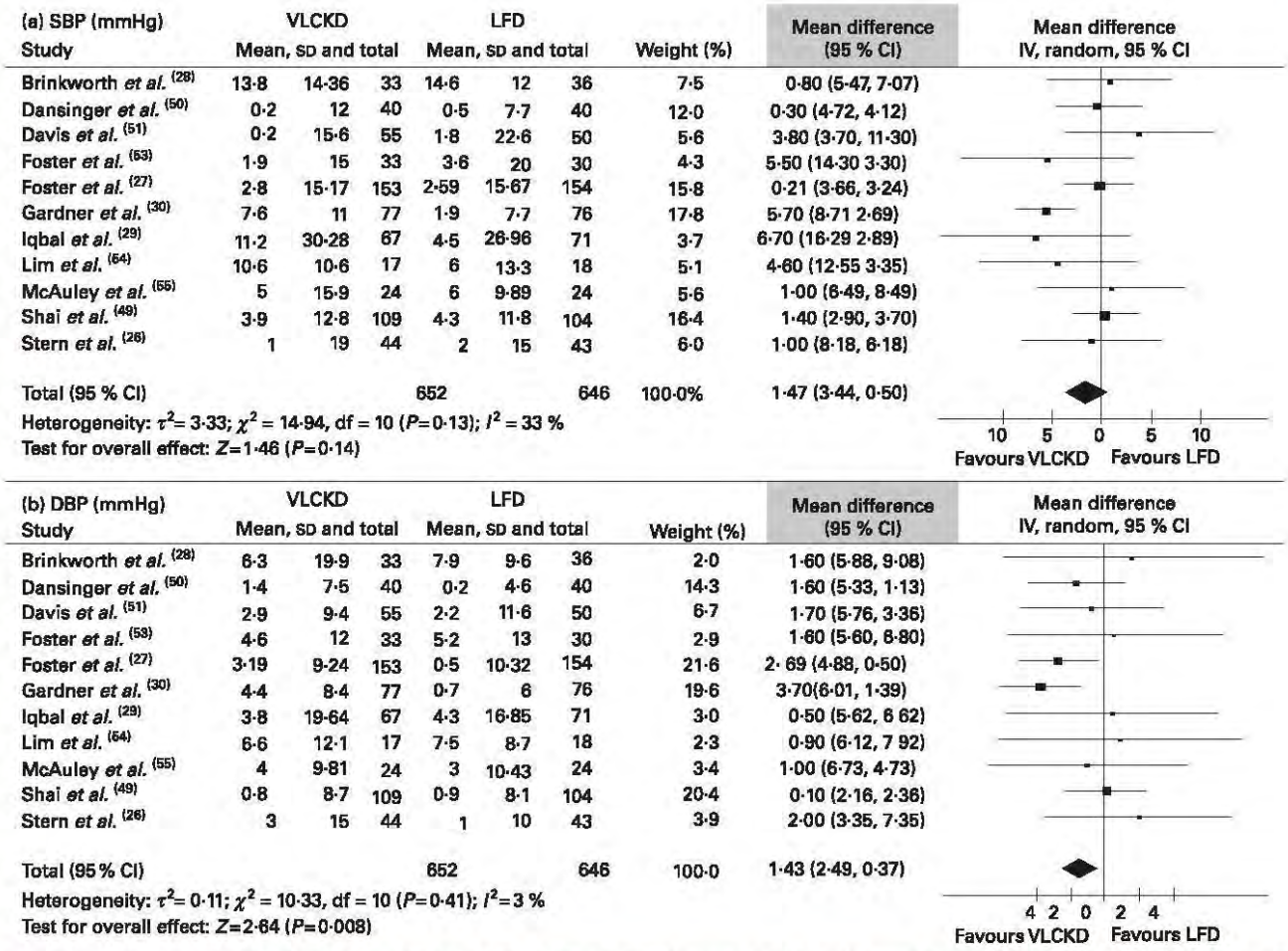

Fig. 3. Absolute changes in (a) systolic blood pressure (SBP) and (b) diastolic blood pressure (DBP). LFD, energy-restricted low-fat diet; VLCKD, very-low -carbohydrate ketogenic diet.

short term, which may explain why meta-analyses of 6-month studies show more impressive results than meta-analyses of longer-term studies, like the present analysis. Greenberg *et al.*[46] found that among dieters, the initial weight reduction in the rst 6 months is the main predictor of both long-term retention and success in weight loss, which may explain the statistically signicant differences observed here.

The Cochrane risk of bias tool was used in the present meta-analysis. Despite being the most recommended tool to assess the risk of bias in randomised controlled trials, it may face some limitations when assessing behavioural or lifestyle interventions, such as dietary ones[47]. These interventions are usually complex, i.e. have multiple components, which deem its delity (the extent to which the intervention has been delivered as planned) an important issue to be assessed[48]. Since the risk of bias tool does not directly address delity, it may be difcult to distinguish between an ineffective intervention and a failed implementation[47].

Upcoming trials should focus on dietary adherence, implementing measures to ensure that individuals adhere to the protocol, as was done by some of the included studies[28,49], permitting better investigation of the long-term effects of a VLCKD. Nevertheless, it is necessary to consider the feasibility of such measures, like those applied by Shai*et al.* [49], where the investigators managed the lunches of all individuals, in a real-life scenario.

In conclusion, the present meta-analysis demonstrates that individuals assigned to a VLCKD achieve signicantly greater long-term reductions in body weight, diastolic blood pressure and TAG, as well as greater LDL and HDL increases when compared with individuals assigned to a LFD; hence, the VLCKD may be an alternative tool against obesity. Investigations beyond that of blood cardiovascular risk factors merit further study.

Supplementary material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S0007114513000548

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A Randomized Trial Comparing a Very Low Carbohydrate Diet and a Calorie-Restricted Low Fat Diet on Body Weight and Cardiovascular Risk Factors in Healthy Women

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Untested alternative weight loss diets, such as very low carbohydrate diets, have unsubstantiated efficacy and the potential to adversely affect cardiovascular risk factors. Therefore, we designed a randomized, controlled trial to determine the effects of a very low carbohydrate diet on body composition and cardiovascular risk factors. Subjects were randomized to 6 months of either an *ad libitum* very low carbohydrate diet or a calorie-restricted diet with 30% of the calories as fat. Anthropometric and metabolic measures were assessed at baseline, 3 months, and 6 months. Fifty-three healthy, obese female volunteers (mean body mass index, 33.6±0.3 kg/m ^{2}) were randomized; 42 (79%) completed the trial. Women on both diets reduced calorie consumption by comparable amounts at 3 and 6 months. The very low carbohydrate diet group lost more weight (8.5±1.0 *vs.* 3.9±1.0 kg; $P<0.001$) and more body fat (4.8±0.67 *vs.* 2.0±0.75 kg; $P<0.01$) than the low fat diet group. Mean levels of blood pressure, lipids, fasting glucose, and insulin were within normal ranges in both groups at baseline. Although all of these parameters improved over the course of the study, there were no differences observed between the two diet groups at 3 or 6 months. β-Hydroxybutyrate increased significantly in the very low carbohydrate group at 3 months ($P=0.001$). Based on these data, a very low carbohydrate diet is more effective than a low fat diet for short-term weight loss and, over 6 months, is not associated with deleterious effects on important cardiovascular risk factors in healthy women. (*J Clin Endocrinol Metab* 88: 16171623, 2003)

THE INCIDENCE OF obesity in the United States has risen continuously over the last several decades, and the associated medical and economic costs to society are substantial (13). Despite considerable desire on the part of obese individuals to lose weight (4) and the clear health benefits of doing so (5), there are currently no proven, effective approaches for meaningful and long-term weight loss for most overweight individuals (2). Dietary strategies supported by the majority of physicians and dietitians, which emphasize restriction of fat intake, are associated with only modest weight loss and poor long-term compliance (6, 7). Given these difficulties and the popular demand for effective weight loss methods, it is not surprising that a number of diet plans have been developed outside the medical and nutritional mainstream that are marketed directly to the public as weight loss strategies.

The very low carbohydrate, high protein diet, promoted extensively by Atkins and others, is one of the most popular of the alternative weight loss approaches (8). The central rationale of this diet is that severe restriction of dietary carbohydrate (<10% of daily caloric intake), with its resulting ketosis, promotes lipid oxidation, satiety, and increased energy expenditure, factors that should promote negative energy balance and weight loss (8). However, these purported responses to very low carbohydrate feeding have not been established. Furthermore, as studies that severely restrict carbohydrate intake have all been of short duration (*i.e.*<6 wk) (916), the clinical benefits of ketogenic diets are unproven.

Because low carbohydrate diets derive large proportions of calories from protein and fat, there has been considerable concern for their potentially detrimental impact on cardiovascular risk (17). Increased consumption of fat, particularly saturated fat, has been linked to increased plasma concentrations of lipids (18), insulin resistance, glucose intolerance (19, 20), and obesity (21, 22). Therefore, it is possible that many Americans could actually suffer adverse health effects by using very low carbohydrate diets in an attempt to lose weight. To evaluate the effects of a very low carbohydrate diet on weight loss and cardiovascular risk factors, we randomized 53 healthy obese women to 6 months of a very low carbohydrate diet or a calorie-restricted, low fat diet conforming to the guidelines currently recommended by the American Heart Association and other expert panels (23).

Subjects and Methods

Subjects

Fifty-three obese females were recruited by advertisement and randomized to the 2 diets based on a prior estimate that 2025 subjects/group would be sufficient to demonstrate a 25% difference in weight loss and a 30% difference in low density lipoprotein (LDL) cholesterol levels between the 2 regimens. Inclusion criteria were age at least 18 yr, moderate obesity (body mass index, 3035), and a stable weight over the preceding 6 months (no weight loss or gain>10% of their body weight). Exclusion criteria were the presence of cardiovascular disease, untreated hypertension, diabetes, hypothyroidism, substance abuse, pregnancy, or lactation. All subjects gave informed consent for the study, which was approved by the University of Cincinnati and Cincinnati Childrens Hospital Medical Center institutional review boards.

Abbreviations: DEXA, Dual energy x-ray absorptiometry; HDL, high density lipoprotein; LDL, low density lipoprotein.

Assessments

Subject assessments were conducted at the General Clinical Research Center of Cincinnati Childrens Hospital Medical Center by trained research nurses. Subjects were screened by medical history and measurements of height, weight, blood pressure, and fasting glucose, and each was given an electrocardiogram. Blood pressure measurements were made by auscultation using an appropriate size cuff with the subject seated quietly. Individuals meeting the criteria for study participation were enrolled in the study by the research assistant or the principal investigator. Subjects gave a sample of fasting blood and had body fat measured by dual energy x-ray absorptiometry (DEXA) using a total body scanner (4500A, Hologic, Inc., San Francisco, CA). DEXA scans were conducted at the body composition core laboratory of the General Clinical Research Center by trained technicians. Each of these measures was repeated after 3 and 6 months of diet.

Study diets

The primary objective of the study was to compare the effects of a very low carbohydrate diet and a calorie-restricted, low fat diet on body composition and cardiovascular risk factors. Therefore, after each block of subjects was assessed, the principal investigator used a random number table to randomly assign those subjects to one of two diets. One group of dieters was instructed to follow an *ad libitum* diet with a maximum intake of 20 g carbohydrate/d (8). It was anticipated that this diet would induce ketosis. After 2 wk of dieting, subjects were permitted to increase their intake of carbohydrate to 40 60 g/d only if self-testing of urinary ketones continued to indicate ketosis. The other group of dieters was instructed on a calorie-restricted, moderately low fat diet with a recommended macronutrient distribution of 55% carbohydrate, 15% protein, and 30% fat. Calorie prescriptions were based on body size and calculated using the Harris-Benedict equation (24).

Two registered dietitians delivered a 3-month intervention aimed at promoting dietary compliance. Group meetings with subjects on the same diet were held biweekly on the University of Cincinnati campus and addressed cooking tips, stress management, behavior modification, and relapse prevention. On alternating weeks, subjects met for individual counseling sessions during which their assigned dietitian reviewed their 3-d food records from the previous week, analyzed by Nutritionist V (First Data Bank, San Bruno, CA), and provided dietary recommendations and positive reinforcement. Subjects were advised to continue their baseline level of activity. To control for possible bias, each dietitian was assigned subjects from each diet group for counseling and alternated as the meeting facilitator for both groups of dieters. Before each weekly session, subjects submitted 3-d food records and were weighed on a single electronic scale (Tanita, Arlington Heights, IL). Blood pressure was measured, and assessment of urinary ketones was performed using Ketostix (Bayer Corp., Elkhart, IN). At the end of the 3-month intervention, subjects were instructed to continue with their weight loss efforts, but without scheduled contact with the dietitians until the 6-month assessment.

Analyses

Determination of total cholesterol, LDL cholesterol, high density lipoprotein (HDL) cholesterol, glucose, insulin, leptin, β-hydroxybutyrate, and triglycerides in fasting plasma were made using conventional methods (25 27). The results of DEXA and biochemical analyses were made by personnel blinded to the group assignment of the subjects.

Statistics

Baseline characteristics were compared between the two groups using *t* tests. To assess the effects of the diets, two-way repeated measures ANOVA, with time as the repeated factor, was performed using the software package SAS (version 8.2, SAS Institute, Inc., Cary, NC). The level of significance was set at 0.05 for testing the main effects of diet and time and the interaction effect. If the main effect was significant, the Bonferroni multiple comparison was implemented to determine the specific differences. If the interaction was significant, the Bonferroni adjustment was used to keep the overall level of significance at 0.05. Differences between groups are indicated only when there is a significant interaction between diet and time. Body weight, biochemical parameters, and DEXA measurements were analyzed for the 42 subjects who completed the study (*i.e.* those for whom follow-up data were available). Body weight was also analyzed for the entire randomized cohort. In this intention to treat analysis, the initial weights for the subjects who withdrew from the study were used as their follow-up weights at 3 and 6 months (*i.e.* an assumption of 0 kg of weight loss). Data are presented as the mean ± SE unless designated otherwise.

Results

Subjects

Subjects were recruited through advertisements from May 2000 through January 2001. Fifty-three obese females (13 African-Americans and 40 Caucasians) were enrolled in the study. Volunteers were enrolled in 3 successive groups of 14, 20, and 19 subjects at 3- to 4-month intervals. Forty-two of the 53 subjects (79%) completed the 6-month study, with 4 dropouts from the very low carbohydrate diet group and 7 dropouts from the low fat diet group (Fig. 1). The majority of subjects discontinuing the study cited difficulty maintaining the scheduled visits as the primary reason, and follow-up measurements were obtained for only 1 of the these women. One subject from each diet group dropped out due to dislike for their assigned diet. Age and anthropometric characteristics of those subjects completing the study are included in Table 1.

Nutrient intake

Subjects randomized to the low fat (n=20) and the very low carbohydrate (n = 22) diet groups consumed similar amounts of calories at the initiation of the diets (1707±104 and 1608±123 kcal respectively) with similar distribution of macronutrients (Fig. 2). Based on the results of the weekly food records, subjects complied with their assigned diets. Although subjects on the carbohydrate-restricted diet were

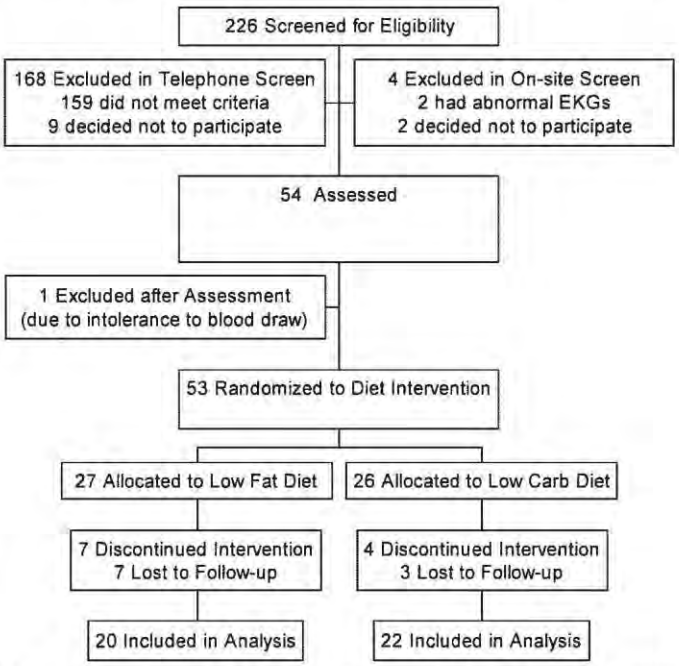

FIG. 1. Flow chart of subjects in the controlled, randomized weight loss trial.

not specifically asked to limit caloric intake as were those on the low fat diet, both groups reported a decrease in caloric intake of approximately 450 calories compared with baseline. Although caloric intakes in the two groups were similar, the proportions of carbohydrate, protein, and fat consumed differed dramatically. At 3 months, caloric intake in the very low carbohydrate diet group was distributed as 15% carbohydrate, 28% protein, and 57% fat. In contrast, the low fat diet group had daily calories distributed as 54% carbohydrate, 18% protein, and 28% fat. At 3 months, the very low carbohydrate diet group consumed significantly less carbohydrate, vitamin C, and fiber and significantly more protein, total fat, saturated fat, monounsaturated fat, polyunsaturated fat, and cholesterol than the low fat diet group ($P<0.01$ for all comparisons). At 6 months, the two groups still differed significantly for most of these measures (Table 2).

Weight and body composition

Body weight and body fat in the low fat and very low carbohydrate groups were similar at baseline (Table 1). After the initiation of the diets, both groups had a decrease in body weight that was more rapid in the earlier weeks of observation and became less pronounced as the study progressed (Fig. 3). The women in the very low carbohydrate group lost an average of 7.6±0.7 kg after 3 months and 8.5±1.0 kg after 6 months of diet. Women following the low fat diet lost 4.2±0.8 and 3.9±1.0 kg at 3 and 6 months, respectively. The amount of weight lost was significantly greater in the very low carbohydrate group compared with the low fat group, whether analyzed as intention to treat with all randomized subjects in the analysis ($P<0.001$ at 3 and 6 months) or with only the subjects who completed the trial (Fig. 3; $P<0.001$ at 3 and 6 months).

Body composition data for the two groups of women are shown in Table 3. Both fat mass and fat-free mass decreased significantly ($P<0.001$) in the two groups over the course of the trial. However, similar to body weight, fat mass and lean body mass decreased significantly more in the very low carbohydrate group compared with the low fat group at both 3 and 6 months ($P<0.01$). The reduced fat mass comprised 50 60% of the weight lost in both groups. There were no changes in bone mineral content over the course of the study.

TABLE 1. Age and anthropometric characteristics before diet initiation of subjects who completed the 6-month study

	Low fat diet group (n=20)		Very low carbohydrate diet group (n=22)		
	Mean (SD)	Range	Mean (SD)	Range	*P*
Age (yr)	43.10 (8.56)	31.08 58.55	44.22 (6.84)	29.01 53.49	0.64
Height (m)	1.65 (0.05)	1.58 1.75	1.66 (0.07)	1.54 1.79	0.58
Weight (kg)	92.31 (6.0)	83.4 105.2	91.20 (8.4)	76.9 113.7	0.61
BMI[a]	34.04 (1.83)	29.57 36.05	33.17 (1.83)	30.87 37.03	0.13
Body fat (%)	41.34 (2.70)	37.3 47.6	41.26 (3.67)	36.2 50.1	0.93

[a] Body mass index (BMI)=weight (kg)/height (m) ^{2}.

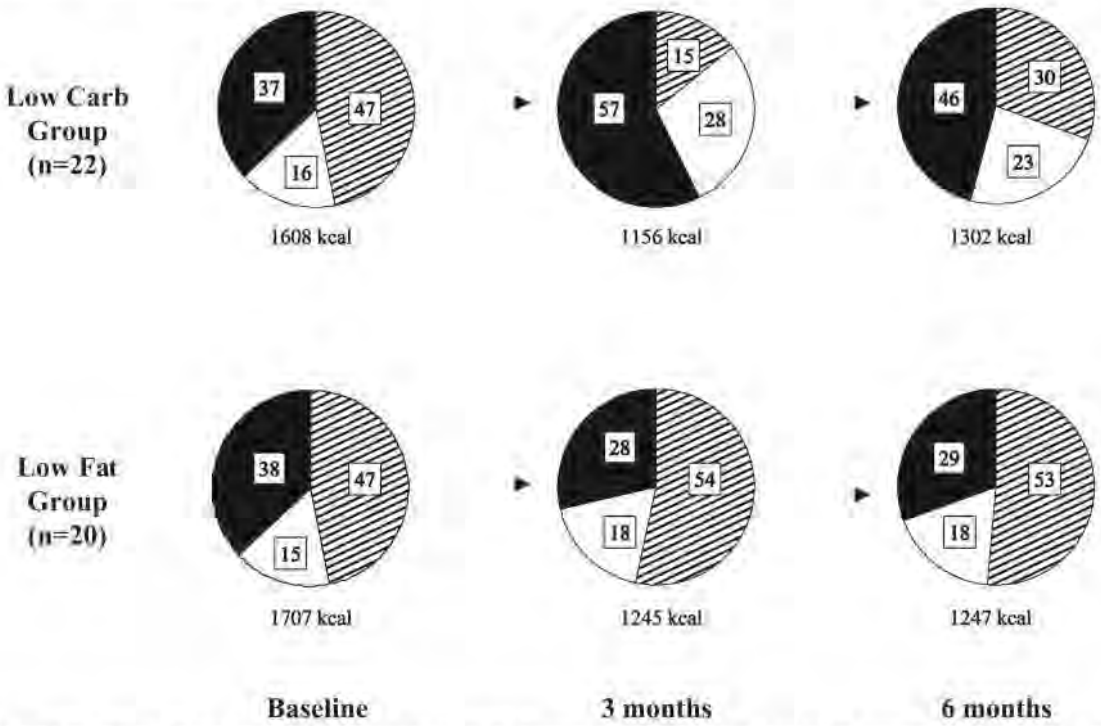

FIG. 2. Mean caloric intake and distribution of macronutrients (as percentage of total kilocalories) of women before and at 3 and 6 months of either very low carbohydrate or low fat diets. *Gray lines*, Carbohydrate; *white*, protein; *black*, fat.

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TABLE 2. Mean nutrient intake of women before and after 3 and 6 months of dieting

	Baseline	3 months	6 months	Recommended intake[a]
Very low carbohydrate diet group (n=22)				
Carbohydrate (g)	188.92	41.13[c]	96.98[c]	≥55% total kcal
Protein (g)	63.32	78.15[c]	74.13[c]	10 15% total kcal
Total fat (g)	65.79	71.32[c]	65.45[c]	≤30% total kcal
Saturated fat (%)	12.4	20.7[c]	17.4[b]	≤10% total kcal
Monounsaturated fat (%)	10.1	20.6[c]	15.8[c]	10% total kcal
Polyunsaturated fat (%)	6.2	9.0[c]	8.2[c]	10% total kcal
Cholesterol (mg)	215.25	460.87[c]	285.44[b]	<300
Vitamin C (mg)	70.28	35.65[c]	58.46	75
Folate (μg)	155.14	139.65	195.89	400
Calcium (mg)	590.81	444.20	739.01	1000
Fiber (g)	12.03	5.27[c]	8.40[c]	20 35
Low fat diet group (n=20)				
Carbohydrate (g)	200.06	169.40	162.88	≥55% total kcal
Protein (g)	66.06	55.93	54.74	10 15% total kcal
Total fat (g)	71.60	39.77	43.13	≤30% total kcal
Saturated fat (%)	12.3	9.9	11.1	≤10% total kcal
Monounsaturated fat (%)	10.1	9.0	7.3	10% total kcal
Polyunsaturated fat (%)	5.8	4.5	3.7	10% total kcal
Cholesterol (mg)	273.51	169.00	182.21	<300
Vitamin C (mg)	76.92	94.18	53.14	75
Folate (μg)	170.95	221.72	193.90	400
Calcium (mg)	607.25	567.19	662.62	1000
Fiber (g)	12.48	13.31	12.35	20 35

[a] Recommended intake for females, 19 50 yr of age.
[b] Denotes values different from the low fat diet group, $P \leq 0.05$.
[c] Denotes values different from the low fat diet group, $P \leq 0.01$.

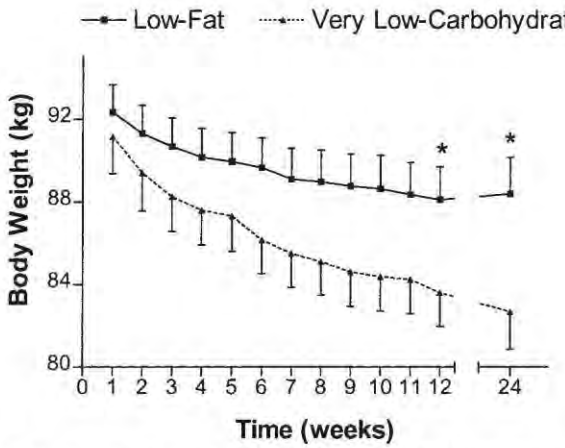

FIG. 3. Mean body weight of women randomized to very low carbohydrate and low fat diets over the course of the 6-month trial. The first time point (wk 1) represents the subjects body weights immediately before randomization. Follow-up for the 2 groups included 17 20 subjects in the low fat group and 19 22 subjects in the very low carbohydrate group. For subjects missing a follow-up visit, their last recorded weight is included in the calculation of the group mean. *, Value different from very low carbohydrate diet group (*i.e.* significant interaction of time and diet), $P<0.001$.

Cardiovascular risk factors

EKG. There were no electrocardiographic abnormalities in any of the subjects during the study.

Blood pressure. The blood pressures in the two groups were within the normal range at the outset of the study and remained so throughout the study (Table 4). Significant differences in blood pressure were not found between the groups during the study.

Plasma lipids. Mean plasma concentrations of total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol were normal in each of the two groups before starting the diets. A significant interaction ($P < 0.05$) was found for plasma triglycerides, but this was probably due to a difference between the groups at baseline. Differences in plasma lipids between the groups were not detected at the 3- or 6-month assessments (Table 4). Significant time effects ($P< 0.01$) for all of the plasma lipids indicated that the subjects improved their lipid profiles during the course of the study, with significant decreases in total cholesterol, LDL cholesterol, and triglycerides at 3 months and significant increases in HDL cholesterol at 6 months (Table 4).

Fasting hormones and substrates. Fasting glucose and insulin did not differ between the two groups at the 3- or 6-month assessments. However, significant time effects for glucose ($P<0.001$) and insulin ($P<0.0001$) indicate that the glucose and insulin levels decreased significantly in the women on both diets over the 6-month study (Table 5). There were no differences in leptin levels between the two groups (Table 5). Yet a significant time effect ($P<0.0001$) shows that plasma leptin levels decreased significantly in both groups of subjects at 3 months (Table 5). A significant difference between the groups was detected for plasma β-hydroxybutyrate, with this ketone increasing significantly more in the very low carbohydrate group at 3 months ($P = 0.0005$; Table 5). Weekly testing of urinary ketones was positive in the majority of subjects on the very low carbohydrate diet and negative in those on the low fat diet.

Discussion

The results of this study demonstrate that a very low carbohydrate diet, taken without a specified restriction of

caloric intake, is effective for weight loss over a 6-month period in healthy, obese women. Compared with the low fat group, who followed a diet conforming to currently recommended distributions of macronutrient calories, the very low carbohydrate group lost significantly more weight, a finding that was apparent both when the women completing the diet were considered alone and when the data were analyzed using intent to treat principles. In addition, despite eating a high percentage of calories as fat and having relatively high intakes of saturated fat and cholesterol, the women in the very low carbohydrate group maintained normal levels of blood pressure, plasma lipids, glucose, and insulin. These data suggest that the deleterious effects of diets containing a high percentage of fat on body weight and cardiac risk factors are mitigated by restriction of caloric intake and associated weight loss.

The subjects recruited for this study were healthy adult women who were moderately obese by current standards. As such they were representative of many American women who embark on weight loss efforts each year using the alternative dietary plans currently marketed in this country. Although compliance with the diets was assessed primarily by dietary records, these data are supported by more objective measures. For example, the average 3-month weight loss in the low fat diet group (~4 kg) is what would be expected for individuals decreasing their daily caloric consumption by about 400 kcal (28), approximately the restriction these women reported making. In addition, there was a significant correlation between reported changes in caloric intake and weight loss ($r = 0.41$; $P < 0.001$). Finally, the presence of measurable ketonemia and ketonuria in the very low carbohydrate group is consistent with severe carbohydrate restriction and was not seen in the low fat dieters. Thus, we believe that the outcomes of this study can be attributed primarily to differences in the prescribed diets of the two groups and are applicable to the large number of obese, but otherwise healthy, American women exploring very low carbohydrate diets.

One conclusion of previous reports on low carbohydrate diets was that the increased weight loss was due to the diuresis that accompanies severe caloric restriction or was due to decreased body water, presumably accompanying depletion of stored glycogen (29, 30). However, these studies were of very short duration, from 1 2 wk in length. Most diets that have a significant restriction of calories cause a sodium diuresis that occurs over the first wk or 2 of their use, and in fact, we noted the most rapid weight loss in both groups over this period. The low fat diet group lost 1.6 kg in the first 2 wk, representing 38% of their mean weight loss during the first 3 months of the study. The very low carbohydrate group lost 3.0 kg during the first 2 wk, or 39% of their mean 3-month weight loss. We analyzed body composition at 3 and 6 months of dieting, well after the expected period of diuresis. Our analysis of body composition showed that the weight lost in the very low carbohydrate diet group consisted of a similar percentage of fat mass as in the low fat diet group. Thus, we think it is very unlikely that differences in weight between the two groups at 3 and 6 months are a result of disproportionate changes in body water in the very low carbohydrate dieters.

The mechanism of the enhanced weight loss in the very low carbohydrate diet group relative to the low fat diet group is not clear. Based on dietary records, the reduction in daily caloric intake was similar in the two groups. For the greater weight loss in the very low carbohydrate group to be strictly a result of decreased caloric consumption, they would have had to consume approximately 300 fewer calories/d over the first 3 months relative to the low fat diet group (28). Although the inaccuracy of dietary records for obese individuals is well documented (31, 32), it seems unlikely that a systematic discrepancy of this magnitude occurred between groups of subjects who were comparably overweight. Therefore, it is difficult to explain the differences in weight loss between the two groups primarily as a function of differing caloric intake. Despite instructions to maintain baseline levels of activity, it is possible that the women in the very low carbohydrate diet group exercised more than those in the low fat diet group. Additionally, it is possible that consuming a very low carbohydrate diet increases resting or postprandial energy expenditure. The possibility that differences in the macronutrient composition of the diet alter energy expenditure is an interesting question that bears further investigation.

Another unexplained, but important, observation was the spontaneous restriction of food intake in the very low carbohydrate diet group to a level equal to that of the control subjects who were following a prescribed restriction of calories. This raises the possibility that the very low carbohydrate diet may have been more satiating. Previous studies have suggested that, calorie for calorie, protein is more satiating than either carbohydrate or fat (33, 34), and it may be that the higher consumption of protein in the very low carbohydrate diet group played a role in limiting food intake. Another explanation for restricted food intake in the very low carbohydrate group is that food choices were probably greatly limited by the requirements of minimizing carbohydrate intake, and that dietary adherence *per se* may have forced caloric restriction due to practical factors. Although it has been proposed that ketosis developing from severe carbohydrate intake contributes to a decrease in appetite (8), this does not seem likely based on our data. Although the women

TABLE 3. Means (and SD) of body composition measures of women before and after 3 and 6 months of dieting

	Very low carbohydrate diet group (n=22)			Low fat diet group (n=20)		
	Baseline	3 months	6 months	Baseline	3 months	6 months
Body fat (g)	37,327.0 (4,787.7)	33,035.2[a] (4,756.9)	32,554.0[a] (5,170.5)	37,827.9 (2,651.8)	35,305.5 (3,602.4)	35,853.3 (4,125.2)
Bone mineral content (g)	2,782.8 (321.2)	2,799.2 (313.7)	2,775.7 (312.7)	2,819.7 (284.7)	2,827.7 (288.2)	2,792.8 (296.7)
Lean body mass (g)	50,385.9 (5,999.9)	47,565.3[a] (5,922.0)	48,418.0[a] (5,871.5)	51,026.8 (5,010.4)	50,181.3 (5,124.9)	50,295.9 (5,197.5)

[a] Denotes value different from the low fat group (*i.e.*, significant interaction of time and diet), $P<0.01$.

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TABLE 4. Means (and SE) of blood pressure and plasma lipid concentrations of women before and after 3 and 6 months of dieting

	Very low carbohydrate diet group (n=22)			Low fat diet group (n=20)		
	Baseline	3 months	6 months	Baseline	3 months	6 months
Blood pressure (mm Hg)	116/79 (3.23/2.69)	112/72 (2.36/2.06)	114/74 (2.82/2.23)	115/75 (2.47/1.99)	116/75 (2.01/1.79)	113/74 (2.41/1.62)
Total cholesterol (mg/dl)	206.32 (6.63)	185.68 (5.64)	205.46 (6.79)	184.45 (6.07)	176.25 (5.87)	182.85 (6.21)
Triglycerides (mg/dl)	148.73[a] (13.41)	92.41 (8.74)	113.86 (15.25)	109.25 (9.49)	101.80 (6.71)	111.00 (12.37)
LDL (mg/dl)	124.86 (5.39)	113.00 (5.34)	124.00 (5.81)	113.80 (6.36)	104.90 (5.97)	107.80 (5.86)
HDL (mg/dl)	51.77 (2.82)	54.09 (2.77)	58.73 (2.57)	48.75 (2.23)	51.05 (3.49)	52.85 (2.58)

To convert to SI units, multiply total cholesterol, LDL-cholesterol, HDL-cholesterol (mg/dl)×0.0259=mmol/liter; multiply triglycerides (mg/dl)×0.1129=mmol/liter.

[a] Denotes value different from the low fat group (*i.e.*, significant interaction of time and diet), $P<0.01$.

following the very low carbohydrate diet developed significant ketonemia, the elevation of circulating β-hydroxybutyrate was mild, well below what is seen in other clinical states of ketosis, such as starvation and diabetic ketoacidosis (26, 35), and was noted only at 3 months. In addition, there was no correlation between the level of plasma β-hydroxybutyrate and weight loss ($r=0.29$; $P=0.43$).

This study provides a surprising challenge to prevailing dietary practice. The current standards for healthy eating include reducing total fat intake to less than 30% of total calories and decreasing saturated fat intake to less than 10%. This recommendation is based on a large body of primarily epidemiological data and is intended to lower plasma cholesterol (23), but has been extended by some experts as a means to decrease the risk of obesity. However, the subjects on the very low carbohydrate diet experienced significantly more weight loss than the low fat group and maintained comparable levels of plasma lipids and other cardiovascular risk factors while consuming more than 50% of their calories as fat and 20% as saturated fat. These data indicate that the role of macronutrient distribution in individuals who are on weight loss diets needs to be further investigated. In particular, it seems likely that in the short term, a decrease in total caloric intake with accompanying weight loss has a greater impact on nutritionally sensitive parameters such as plasma lipids than do the macronutrient constituents of the diet.

The results of this study are applicable to healthy persons, but extension of our findings to subjects with established cardiovascular risk factors should not be made without further careful investigation. The mean levels of blood pressure, glucose, and plasma lipids in our subjects were normal and, in fact, lower than the average values for American adults (36). It is possible that very low carbohydrate diets, with high relative intakes of protein and fat, would have deleterious effects in subjects with hyperlipidemia, diabetes, or other metabolic disorders.

Although advocates for very low carbohydrate diets are likely to embrace the results of this study, several points of caution need to be emphasized. First, a single study of a specific dietary regimen cannot provide a full assessment of safety and efficacy. Despite this study being the longest randomized, controlled trial of a very low carbohydrate diet reported, our results are still limited by the 6-month time frame. Whether the very low carbohydrate diet will produce sustained weight loss and continued improvement in cardiovascular risk factors over longer periods of time remains to be determined; the gradual increase in carbohydrate consumption in the final 3 months of the study suggests that some degree of recidivism is likely in persons on this diet. In addition, increased dietary fat has been linked to certain types of cancer (37) and may have effects on cardiovascular health beyond the risk factors assessed in this study. There was also a low intake of calcium and fiber in the very low carbohydrate group that would need to be addressed if this diet were to be used for longer periods. Finally, long-standing ketosis has been associated with myocardial dysfunction in children after a ketogenic diet to treat intractable seizures (38). Despite these concerns, the present results indicate that there are important, interesting, and poorly understood effects of severe carbohydrate restriction that warrant further

TABLE 5. Means (and SE) of substrate and hormone concentrations of women before and after 3 and 6 months of dieting

	Very low carbohydrate diet group (n=22)			Low fat diet group (n=20)		
	Baseline	3 months	6 months	Baseline	3 months	6 months
Glucose (mg/dl)	99.1 (2.6)	93.8 (2.7)	90.1 (2.1)	91.1 (2.1)	90.5 (2.5)	87.5 (2.0)
Insulin (μU/ml)	16.9 (1.8)	11.6 (1.2)	14.4 (1.4)	23.9 (2.34)	18.1 (2.5)	18.4 (2.1)
Leptin (ng/ml)	25.43 (1.49)	16.23 (1.09)	21.68 (1.49)	30.08 (1.88)	25.35 (1.82)	29.40 (2.58)
β-hydroxybutyrate (mg/dl)	1.04 (0.31)	4.30[a] (1.10)	1.52 (0.51)	1.01 (0.40)	1.17 (0.27)	1.14 (0.44)

To convert to SI units, multiply glucose (mg/dl)×0.0555=mmol/liter; multiply insulin (μU/ml)×6.945=pmol/liter; multiply β-hydroxybutyrate (mg/dl)×96.05= μmol/liter.

[a] Denotes value different from the low fat group (*i.e.*, significant interaction of time and diet), $P<0.01$.

investigation as we seek effective therapeutic strategies to manage the epidemic of obesity.

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SURGICAL ENDOSCOPY
and Other Interventional Techniques

The effect of a low-carbohydrate diet on the nonalcoholic fatty liver in morbidly obese patients before bariatric surgery

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Abstract
Background: Bariatric surgery may be complicated by enlargement of the liver, especially of the left lobe, caused by nonalcoholic fatty liver disease often present with morbid obesity.
Methods: The effect of a very low carbohydrate diet for 4 weeks before surgery on liver density and volume was assessed in 14 candidates for bariatric surgery. Computed tomography (CT) scans were performed before and at termination of the diet period.
Results: The CT scans clearly showed a significant increase in mean liver density ($p = 0.06$) and a decrease in mean liver volume ($p = 0.01$). The increased mean density of the left lobe was markedly greater than that of the right lobe.
Conclusions: The findings show that 4 weeks of a very low carbohydrate diet reduces liver fat content and liver size, particularly of the left lobe. This approach may render bariatric surgery or any foregut operations less difficult in morbidly obese patients and may be a useful treatment for nonalcoholic fatty liver disease.

Key words: Bariatric surgery — Low-carbohydrate diet — Nonalcoholic fatty liver

In the Western world, the prevalence of obesity is increasing at an alarming rate and has virtually become a plague. Obesity substantially increases morbidity, impairs quality of life, decreases life expectancy, and is linked to many chronic health problems [21]. Morbid obesity often is associated with nonalcoholic fatty liver disease (NAFLD).

The preferred treatment is bariatric surgery [18], using either an open or laparoscopic procedure. A common difficulty lies in the fatty enlargement of the left lobe of the liver, which acts to obscure the operating field, interfering with adequate visualization of the upper part of the stomach and the gastroesophageal area. Moreover, the fibrofatty liver may bleed or even fracture during the traumatic retraction necessary to expose the operating field [6], thus adding to the difficulty of completing a successful procedure. Indeed, it is reported in different studies that liver biopsies taken from obese patients who were candidates for bariatric surgery showed up to 90% fatty changes [10].

Improvement in liver function with weight loss was first reported in 1986 by Eriksson et al. [4]. Luyckx et al. [10] in 1998 and Mattar et al. [11] in 2005 showed that postgastroplasty weight loss reduced liver steatosis. Fris [6] found that a low-energy diet for 2 weeks before bariatric surgery reduced liver size, as measured by ultrasound examination, and Nomura et al. [13] demonstrated a reduction in liver volume, as measured by CT scan, in overweight patients who had been on a low-calorie diet for 3 months.

Other researchers [5,20] have compared the effect of a low-carbohydrate diet with that of a low-calorie diet, finding that weight loss is greater with the low-carbohydrate diet. Volek et al. [20] reported that a low-carbohydrate diet had a greater effect than a low-fat diet on weight loss and body composition in overweight patients. Very recently, Lewis et al. [9] reported that magnetic resonance imaging (MRI) studies demonstrated a marked reduction in liver volume and fat content after 6 weeks of a very low calorie diet. There is,

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however, no data available showing the effect of a low-carbohydrate diet on steatosis in obese patients.

The current study used CT scans, a proven method for documenting fatty infiltration of the liver, to determine whether a low-carbohydrate diet instituted 4 weeks before bariatric surgery can reduce the liver volume, thus not only making surgery easier and safer, but possibly also demonstrating its potential usefulness in the treatment of NAFLD in obese patients.

Material and methods

Patients

Initially, the study enrolled 22 morbidly obese patients ages 18 to 60 years, all candidates for bariatric surgery (laparoscopic gastric banding). The protocol for the study was approved by the ethics committee of the hospital, and informed consent was obtained from all the patients. The criteria for inclusion in the study required a body mass index (BMI) greater than 35 kg/m^2 with associated comorbidity or a BMI exceeding 40 kg/m^2.

Each patient was subjected to a thorough physical examination. Before and after institution of the low-carbohydrate diet, weight was measured, blood samples were obtained to determine liver function and plasma lipids, and CT scans of the upper abdomen were performed.

Computed tomography

All CT examinations were performed using a Multi Detector CT, Phillips, Haifa, Israel, MX8000. Using no oral or intravenous contrast material, 3×1.5 axial slices were taken from the level of the diaphragm to the iliac crests. The volume and density of the liver were assessed on the postprocessing workstation (MX View Processing Workstation; Picker Medical Systems, Haifa, Israel). Liver and spleen density values were determined from images displayed at a standardized setting (window width, 200 HU; level, 50 HU), with region-of-interest markers set over segments 2, 3, 4A, and 4B (for the left lobe of the liver) and segments 5, 6, 7 and 8 (for the right lobe).

The spleen, known to be almost devoid of fat, served as a reference organ, with two density values obtained: one from the superior aspect and one from the inferior aspect. The mean density was calculated for each organ, including separate calculations for the right and left lobes of the liver. The region-of-interest area was kept constant for each patient. Also calculated was the ratio of liver density to spleen density, considered to be a more accurate indicator of normal and abnormal liver than the absolute CT numbers. The whole-liver volumes were calculated from the axial image data set using the postprocessing graphic workstation. The volume of each liver lobe could not be assessed separately because no contrast material was injected.

Dietary intervention

After the initial CT scan, each patient met with the clinical dietician and received instructions regarding the low-carbohydrate diet and maintenance of a meticulous daily food intake diary, to be submitted weekly for supervision by the dietician. The nutritional program was based mainly on proteins and fats, with carbohydrates limited to approximately 30 g daily, but with no limitation of calories. There was no restriction of low-carbohydrate foods, including all types of meat and fish, eggs, low-carbohydrate dairy products, walnuts and almonds, and oils of all kinds. There were no restrictions as to the type of fat, whether saturated or unsaturated, or the cholesterol content of foods.

The patients were instructed to consume a large amount of water or low-carbohydrate drinks. They were provided with charts listing carbohydrate levels in vegetables and dairy products, and also with specific lists of appropriate foods and meal plans compatible with their individual preferences.

Table 1. Daily intake of dietary energy and nutrients during the low-carbohydrate diet[a]

Nutrient	
Energy (Kcal)	1520 ± 285
Protein (g)	110 ± 36
Protein (%)	29 ± 9
Carbohydrate (g)	54 ± 22
Carbohydrate (%)	14 ± 4
Total fat (g)	94 ± 22
Total fat (%)	56 ± 13
Monounsaturated fat (g)	30 ± 9
Polyunsaturated fat (g)	30 ± 10

[a] Values are mean ± standard deviation

During the weekly session with the dietician, the patient was weighed, and the food intake diary was reviewed to affirm adherence to the regimen. At completion of the 4-week period of low-carbohydrate diet, a repeated CT scan was performed, and blood samples were obtained.

Statistical analysis

Data are presented as mean ± standard deviation. Pearson correlation coefficients (r) and significance (p) were calculated between the variants. A paired t-test was performed to determine statistically significant differences in mean parameters before and after the low-carbohydrate diet. A p value of 0.05 or less was considered statistically significant.

Results

Of the 22 patients initially enrolled in the study, 8 were withdrawn for the following reasons: 5 for inability to tolerate the restricted diet, 2 because of a technical problem with the initial CT scan, and 1 because the CT scan had shown a large adrenal mass requiring further evaluation. Thus, 14 patients (9 women and 5 men, ages 24 to 45 years) completed the study and eventually underwent surgery. Their mean BMI was 45.9 kg/m^2 (range, 40.2–56.6 kg/m^2).

One of the women underwent a follow-up CT scan 3 months after her baseline CT scan, but 1 month after starting the diet. Analysis of the dietary records showed a mean intake of 1,520 ± 285 kcal/day (range, 1,109–1,922 kcal/day): 14% ± 4% contributed by carbohydrates, 29% ± 9% contributed by protein, and 56% ± 13%contributed by fat (Table1).

At the end of the diet period, a significant decrease in body weight and BMI was found. There was no significant change in levels of triglycerides or cholesterol, but the high-density lipoprotein (HDL) level had decreased significantly. No significant effect on liver function parameters was observed (Table2).

Figure1shows sample CT studies conducted before and after the diet period, clearly picturing the difference in liver density and volume. Table3presents the mean density values for the whole liver and for each lobe, as well as the mean volumes for the whole liver before and after the diet period. Although the increased density of the whole liver was not statistically significant, that of the left lobe was always greater than that of the right lobe, which was statistically significant.

Table 2. Variables analyzed before and after the low-carbohydrate diet and their significance[a]

	Before	After	pValue
Weight (kg)	129.19 ± 15.91	124.45 ± 16.24	0.0018
BMI (Kg/m^2)	45.92 ± 5.51	43.58 ± 4.91	0.0014
Cholesterol	191.54 ± 42.10	173.33 ± 36.48	NS
LDL	115.83 ± 38.09	104.73 ± 29.11	NS
HDL	47.81 ± 13.52	39.57 ± 12.77	0.0203
Triglycerides	138.38 ± 39.3	168.67 ± 106.60	NS
ALT	26.36 ± 13.89	27.25 ± 13.18	NS
AST	37.21 ± 28.57	38.25 ± 31.83	NS
Glucose	100.57 ± 24.71	96.75 ± 19.05	NS

BMI, body mass index; NS, not statistically significant; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase

[a] The cholesterol, triglycerides and glucose units are mg/dl; the ALT and AST units are U/l

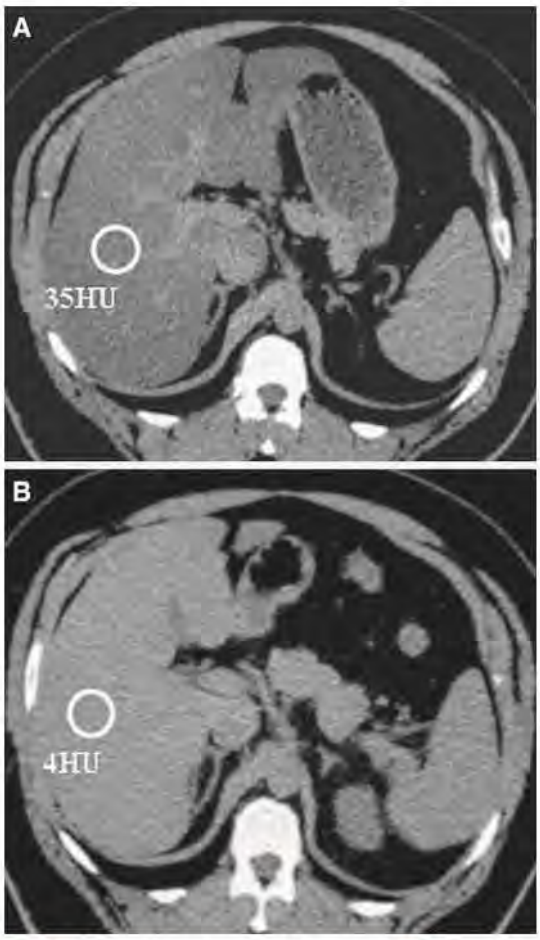

Fig. 1. Noncontrast computed tomography (CT) scan at the level of the liver before the low-carbohydrate diet is started (A) and at termination of the diet after 4 weeks (B).

The spleen showed no significant change in density, but the ratio of liver density to spleen density increased significantly ($p = 0.06$). The ratio for the left lobe also showed a significant increase ($p = 0.044$), whereas the increase for the right lobe was not significant.

The mean liver volume decreased significantly, showing a change of 8.1%. The change in liver volume was correlated with the change in liver densities ($r = -0.54$;$p = 0.04$), but not with the change in body weight ($r = 0.48$;$p = 0.1$) or BMI.

Ease of access during the surgical procedure

Although no objective assessment could be made during the surgical procedure, there was the clear impression in all cases that the reduction in liver volume, particularly of the left lobe, facilitated access to the region of the gastroesophageal junction, with no difficulty encountered during the necessary retraction.

Discussion

Obesity is considered to be a major public health problem, particularly, but not exclusively, in the Western world, with a rise in global prevalence. In United States, it was found that for the years 1999–2000, the prevalence of overweight was 64.5%, whereas that of extreme obesity (BMI≥40) was 4.7%[21] Up to 90%of morbidly obese patients have been found to suffer from steatosis [3], which may eventually deteriorate to cirrhosis and liver failure. Luyckx et al. [10] reported that liver biopsies obtained from candidates for bariatric surgery showed up to 90%fatty changes. Papadia et al. [14] in their study of 1,000 liver biopsies from candidates for bariatric surgery found that in 26%there was steatosis exceeding 70%. Regression analysis showed a correlation of steatosis with body weight and BMI.

Obesity is highly associated with NAFLD, conferring a greater risk of histologically advanced disease. Liver disease is found to be third among the leading causes of death in the natural history of NAFLD, although the absolute risk is low (1.7%) [1]. Treatment options for NAFLD include dietary weight loss and bariatric surgery.

Bariatric surgery is a technically challenging procedure prone to surgical complications. The fatty enlarged liver not only causes difficulty in exposure of the stomach, but also may bleed or even fracture during the retraction necessary to expose the operating field [6,16]. Such complications tend to occur more frequently in patients with a higher BMI [2]. Our working hypothesis was that a low-carbohydrate diet would lead to shrinkage of the liver, thereby improving the surgical operability of the obese patient.

Most of the dietary options propose a low-fat diet, although no data exist to date on the effect of a low-carbohydrate diet on NAFLD [7].

Support for the potential efficacy of a low-carbohydrate diet is provided by the finding of Solga et al. [19] that a high-carbohydrate intake could worsen histopathologic findings in NAFLD. Furthermore, Schwartz et al. [17] found that a high carbohydrate intake increased hepatic de novo lipogenesis, whereas a high fat intake decreased hepatic de novo lipogenesis in obese hyperinsulinemic individuals, as compared with obese normoinsulinemic individuals.

Our study was designed to investigate the effect of a low-carbohydrate diet on the deposition of fat in the

Table 3. Liver density, the ratio of liver density to spleen density, and the volume of the liver before and after diet[a]

	Before	After	*p*Value
Whole-liver density (HU)	39.33 ± 14.04	43.46 ± 8.16	NS
Density of left lobe of the liver (HU)	40.6 ± 15.12	45.62 ± 8.72	0.07
Density of the right lobe of the liver (HU)	38.14 ± 13.27	41.7 ± 8.05	NS
Density of the spleen (HU)	43.39 ± 4.51	42.21 ± 4.0	NS
Liver/spleen density	0.9 ± 0.33	1.04 ± 0.22	0.06
Left lobe liver/spleen density	0.9 ± 0.31	1.08 ± 0.22	0.044
Right lobe liver/spleen density	0.88 ± 0.31	0.99 ± 0.22	NS
Liver volume (ml)	2718 ± 422.61	2495 ± 414.10	0.01

HU, hounsfield units; NS, not statistically significant
[a] Values are mean ± standard deviation

liver and its effect on liver volume in morbidly obese patients scheduled to undergo bariatric surgery. Fat deposition, its distribution in the liver, and liver volume were assessed using CT studies. Fat deposition was characterized by a low attenuation within the liver as compared with that of the spleen, which served as an internal norm [15].

The results obtained clearly showed that fatty infiltration of the liver in morbidly obese patients is a reversible process, as demonstrated by the increase in liver attenuation and the reduction in volume after the short-term low-carbohydrate diet. Furthermore, there was a significant difference between the right and left lobes, with the left lobe showing a significantly larger increase in attenuation than the right lobe.

These findings are in agreement with those reported by Nomura et al. [13] from their study of CT features after a low-calorie diet. The fact that the loss of fat is more prominent in the left lobe of the liver has important implications for any surgical procedure performed in the area of the upper stomach and gastroesophageal junction. Indeed, in all the surgical procedures performed for the 14 patients in our study, the surgeons were clearly impressed with the greater ease of access and technical performance.

There is no specific treatment currently available for hepatic steatosis, and dietary measures appear to be the only means to achieve any improvement in this condition. As noted earlier, various dietary approaches have been used toward this goal, most of them based on low-calorie regimens. Recently, Nakamuta et al. [12] used a protein-rich diet combined with exercise and bezafibrate to lessen steatosis in potential donors for living-donor liver transplantation. Hwang et al. [8] placed potential donors on a similar regimen of diet and exercise, without medication.

Preoperative weight loss also has been achieved for high-risk patients by insertion of an intragastric balloon for a few months before bariatric surgery. Alfalah et al. [2] reported an excess weight reduction of 10%within 3 months after insertion of an intragastric balloon. However, there are no data regarding the effect of this procedure on the reduction in liver size and its influence on the fatty liver.

The results achieved in our study with a short-term low-carbohydrate diet indicate that this may well prove to be an effective treatment strategy for NAFLD in addition to facilitation of the surgical procedure when surgery must be performed for morbidly obese patients.

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Critical Review

Dietary carbohydrate restriction as the first approach in diabetes management: Critical review and evidence base

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ABSTRACT

The inability of current recommendations to control the epidemic of diabetes, the specific failure of the prevailing low-fat diets to improve obesity, cardiovascular risk, or general health and the persistent reports of some serious side effects of commonly prescribed diabetic medications, in combination with the continued success of low-carbohydrate diets in the treatment of diabetes and metabolic syndrome without significant side effects, point to the need for a reappraisal of dietary guidelines. The benefits of carbohydrate restriction in diabetes are immediate and well documented. Concerns about the efficacy and safety are long term and conjectural rather than data driven. Dietary carbohydrate restriction reliably reduces high blood glucose, does not require weight loss (although is still best for weight loss), and leads to the reduction or elimination of medication. It has never shown side effects comparable with those seen in many drugs. Here we present 12 points of evidence supporting the use of low-carbohydrate diets as the first approach to treating type 2 diabetes and as the most effective adjunct to pharmacology in type 1. They represent the best-documented, least controversial results. The insistence on long-term randomized controlled trials as the only kind of data that will be accepted is without precedent in science. The seriousness of diabetes requires that we evaluate all of the evidence that is available. The 12 points are sufficiently compelling that we feel that the burden of proof rests with those who are opposed.

> At the end of our clinic day, we go home thinking, The clinical improvements are so large and obvious, why dont other doctors understand? Carbohydrate restriction is easily grasped by patients: Because carbohydrates in the diet raise the blood glucose, and as diabetes is defined by high blood glucose, it makes sense to lower the carbohydrate in the diet. By reducing the carbohydrate in the diet, we have been able to taper patients off as much as 150 units of insulin per day in 8 d, with marked improvement in glycemic control—even normalization of glycemic parameters.
>
> —Eric Westman, MD, MHS [1].

Introduction

Reduction in dietary carbohydrate as a therapy for diabetes has a checkered history. Before and, to a large extent, after the discovery of insulin, it was the preferred therapeutic approach [2]. Only total reduction in energy intake was comparable as an effective dietary intervention. The rationale was that both type 1 and type 2 diabetes represent disruptions in carbohydrate metabolism. The most salient feature of both diseases is hyperglycemia and the intuitive idea that reducing carbohydrate would ameliorate this symptom is borne out by experiment with no significant exceptions. Two factors probably contributed to changes in the standard approach. The ascendancy of the low-fat paradigm meant that the fat that would replace the carbohydrate that was removed was now perceived as a greater threat, admittedly long term, than the immediate benefit from improvement in glycemia. The discovery of insulin may have also cast diabetes—at least type 1—as a hormone-deficiency disease where insulin (or more recent drugs) were assumed to be a given and dietary considerations were secondary. For these and other reasons, dietary carbohydrate holds an ambiguous position as a therapy.

Although low-carbohydrate diets are still controversial, they have continued to demonstrate effectiveness with little risk and good compliance. At the same time, the general failure of the low-fat paradigm to meet expectations, coupled with continuing reports of side effects of different drugs, indicates a need for reevaluation of the role for reduction in carbohydrate. The current issue seems to be whether we must wait for a long-term randomized controlled trial (RCT) or whether we should evaluate all the relevant information. Practical considerations make it virtually impossible to fund a large study of nontraditional approaches. In any case, the idea that there is one kind of evidence to evaluate every scientific question is unknown in any science. Here we present 12 points of evidence supporting the use of low-carbohydrate diets as the first approach to treating type 2 diabetes and as the most effective adjunct to pharmacology in type 1. They are proposed as the most well-established, least controversial results. It is not known who decides what constitutes evidence-based medicine but we feel that these points are sufficiently strong that the burden of proof rests on critics. The points are, in any case, intended to serve as the basis for improved communication on this topic among researchers in thefield, the medical community, and the organizations creating dietary guidelines. The severity of the diabetes epidemic warrants careful and renewed consideration of our assumptions about the diet for diabetes.

Definitions

A lack of agreed on definitions for *low-carbohydrate diet* has been a persistent barrier to communication. We propose the definitions in Table 1 to eliminate ambiguity. Each definition is based on use in multiple publications by those authors who have performed the experimental studies [3 6].

We recognize that levels of carbohydrate tolerance vary between individuals and even in one person over time. For example, a very low-carbohydrate ketogenic diet (VLCKD) is defined as comprised of 20 to 50 g/d carbohydrate, but because of individual variability, ketosis (blood ketone bodies >0.5 mM) may not occur.

12 Points of evidence

Point 1. Hyperglycemia is the most salient feature of diabetes. Dietary carbohydrate restriction has the greatest effect on decreasing blood glucose levels

Both type 1 and type 2 diabetes are defects in the response to food, particularly to carbohydrates. The associated hyperglycemia is both the most characteristic symptom and the cause of downstream sequelae including insulin effects and generation of advanced glycation end products (AGEs). The most

Table 1
Suggested definitions for different forms of low-carbohydrate diets*

- Very low-carbohydrate ketogenic diet (VLCKD)
  - Carbohydrate, 20–50 g/d or <10% of the 2000 kcal/d diet, whether or not ketosis occurs. Derived from levels of carbohydrate required to induce ketosis in most people.
  - Recommended early phase (“induction”) of popular diets such as Atkins Diet or Protein Power.
- Low-carbohydrate diet: <130 g/d or <26% total energy
  - The ADA definition of 130 g/d as its recommended minimum.
- Moderate-Carbohydrate Diet: 26%–45%
  - Upper limit, approximate carbohydrate intake before the obesity epidemic (43%).
- High-Carbohydrate Diet: >45%
  - Recommended target on ADA websites.
  - The 2010 Dietary Guidelines for Americans recommends 45%–65% carbohydrate. The average American diet is estimated to be ~49% carbohydrate.
  - Carbohydrate Consumption (NHANES)†:
    - Men
      - 1971–1974: 42% (~250 g for 2450 kcal/d)
      - 1999–2000: 49% (~330 g for 2600 kcal/d)
    - Women
      - 1971–1974: 45% (~150 g for 1550 kcal/d)
      - 1999–2000: 52% (~230 g for 1900 kcal/d)

ADA, American Diabetes Association; NHANES, National Health and Nutrition Examination Survey
* Derived from Accurso et al. [3] and references therein.
† NHANES is a series of studies conducted since 1960 that monitors >5000 people.

obvious glycation product, hemoglobin A_{1c} (HbA_{1c}) is widely taken as diagnostic. Glycemic control remains the primary target of therapy in patients with type 1 and type 2 diabetes. It is universally accepted that dietary carbohydrate is the main dietary determinant of blood glucose [7] and restriction shows the greatest reduction in postprandial and overall glucose concentrations as well as HbA_{1c} [3,6,8–14]. Whereas defects in repression of gluconeogenesis and glycogenolysis are the major causes of hyperglycemia [8,15], carbohydrate is by far the greatest dietary contributor to blood sugar rises and, as expected, dietary carbohydrate restriction reliably reduces glucose profile.

Hussain et al. [14], for example, compared a VLCKD with a low-calorie diet over a 24-wk period in 102 diabetic and 261 nondiabetic individuals. As shown in Figure 1, blood glucose dropped more dramatically in the VLCKD group than in those given the low-calorie diet. In the patients with type 2 diabetes, however, after 24 wk, the average blood glucose level was approximately 1 mM lower than in the low-calorie diet group. More significantly, the VLCKD group approached normal blood sugar levels after 24 wk, whereas the low-calorie groups blood glucose concentration leveled out at 16 wk and remained elevated. In the normal patients, blood glucose was already at normal levels, and the VLCKD produced only a small effect.

The second panel in Figure 1 shows the effect of the two diets on HbA_{1c} levels. At 24 wk, patients with diabetes given the VLCKD achieved an HbA_{1c} of 6.2%, whereas the average HbA_{1c} in the low-calorie diet group remained >7.5%.

Point 2. During the epidemics of obesity and type 2 diabetes, caloric increases have been due almost entirely to increased carbohydrates

Data from the National Health and Nutrition Examination Surveys (NHANES) [16] indicate a large increase in carbohydrates as the major contributor to caloric excess in the United States from 1974 to 2000 (Fig. 2). From the time of the first NHANES study (1974) to the last (2000), dietary carbohydrate in men rose from 42% to 49% of calories. For women, carbohydrate rose from 45% to 52%. The absolute amount of fat decreased for men during this period and showed only a slight increase for women. The inset to the Figure 2 reveals the rise, during this period, of the incidence of type 2 diabetes to its current near epidemic proportions [17]. More recently, one study [18] analyzed U.S. Department of Agriculture availability data and found that the absolute fat availability had increased slightly, but, as shown in the NHANES data [19], the increase in carbohydrate was the predominant change.

These epidemiologic measurements are supported by biochemical mechanisms. Continued stimulation of insulin production can lead to an anabolic state that favors triglyceride (TG) synthesis over lipolysis and generation of TG-rich lipoproteins [5].

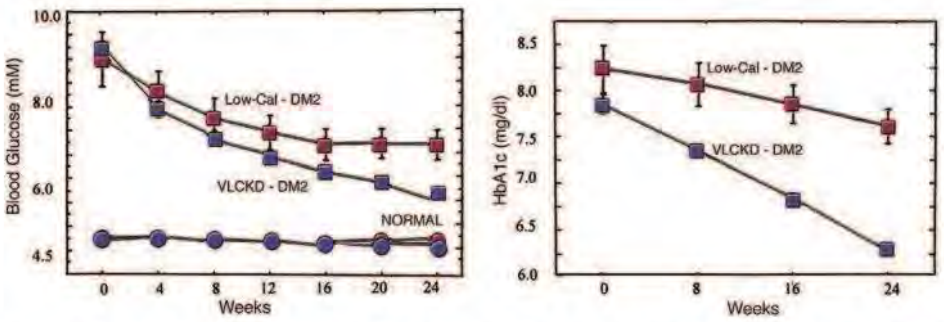

Fig. 1. Effect of low-calorie versus low-carbohydrate ketogenic diet in type 2 diabetes. Redrawn from [14]. DM2, type 2 diabetes mellitus; VLCKD, very low-carbohydrate ketogenic diet.

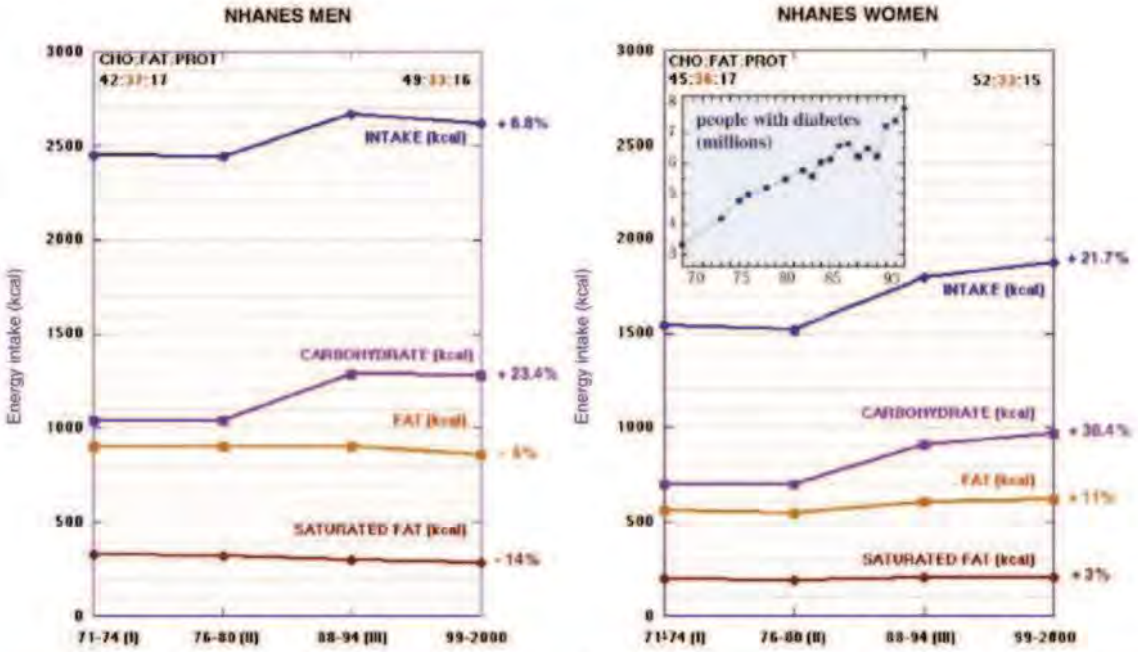

Fig. 2. Macronutrient consumption during the epidemic of obesity and type 2 diabetes. Data from the National Health and Nutrition Examination Survey (NHANES) by year, and from Centers for Disease Control and Prevention [19]. Inset: Incidence of diabetes (millions of people with diabetes by indicated year). Data from [17]. CHO, carbohydrate; Prot, protein.

Additionally, accumulation of fat in the liver and, secondarily, in the pancreas, create self-reinforcing cycles that are believed to contribute to the onset of type 2 diabetes. Fatty liver leads to impaired fasting glucose metabolism and increased export of very-low-density lipoprotein (LDL)-TG, which, in turn, increases fat delivery to all tissues, including the insulin-producing pancreatic islets. These liver and pancreas cycles lead to steadily decreasing β-cell function [20]. The hepatic lipogenesis transcriptional program is activated both directly and indirectly by carbohydrate ingestion. Sterol regulatory element-binding protein and carbohydrate-responsive element-binding protein are major transcriptional regulators that are activated by carbohydrate signal to stimulate de novo hepatic lipogenesis. Uncontrolled de novo lipogenesis causes hepatic steatosis, which is closely associated with the onset of obesity, insulin resistance, and type 2 diabetes [13].

Whatever the extent to which the correlation between carbohydrate consumption and diabetes is causal, the lack of association between the levels of dietary fat and diabetes in humans is of real significance. A lack of association is generally considered strong evidence for a lack of causality.

Point 3. Benefits of dietary carbohydrate restriction do not require weight loss

As described in point 1, low-carbohydrate diets generally perform better than explicitly low-calorie diets but because such trials are frequently hypocaloric by design or, by virtue of the spontaneous reduction of intake, it is not always possible to exclude the direct effect of calorie restriction or indirect hormonal effects due to feedback from changes in the adipocytes. This is an important consideration in that it is well established that the symptoms of type 2 diabetes improve with weight loss. Insofar as the American Diabetes Association and other agencies recommend low-carbohydrate diets, it is usually solely for weight loss. Many people with type 2 diabetes, however, are not overweight and, conversely, many overweight people never develop type 2 diabetes. People with type 1 are not generally overweight although, at least anecdotally, the weight gain associated with insulin therapy may be a reason for poor compliance [21,22]. Additionally, several lines of investigation support the idea that weight loss is not required for improvement in glycemic control and other symptoms in diabetes.

A series of well-designed experiments have been carried out that demonstrated improvements in glycemic control and hormonal and lipid parameters under conditions where patients were maintained at constant weight [9–11]. The most effective, 20%, was the lowest level of carbohydrate studied, although still lower might have been more effective. Results from a recent study [9] are shown in Figure 3. Although the experimental protocol, described by the authors as a low-bioavailable glucose (30% of energy) diet, did not conform to the definitions in Table 1, they indicate that improvement in glycemic control is possible without weight loss, even with only slightly lower carbohydrate. Studies in which weight is lost and glycemic control is attained do not show any correlation between the two outcomes (Fig. 4B). Given the difficulties that most people have losing weight, this factor alone provides an obvious advantage to low-carbohydrate diets.

Point 4. Although weight loss is not required for benefit, no dietary intervention is better than carbohydrate restriction for weight loss

The previous point emphasizes that low-carbohydrate diets provide benefit in the absence of weight loss. Nonetheless, such diets consistently outperform low-fat diets for whatever time period they are compared and frequently show dramatically better results. Figure 4 shows two examples in people with diabetes. One study [23] randomly allocated 26 people to either a low-carbohydrate diet (40 g/d carbohydrate) or a healthy-eating

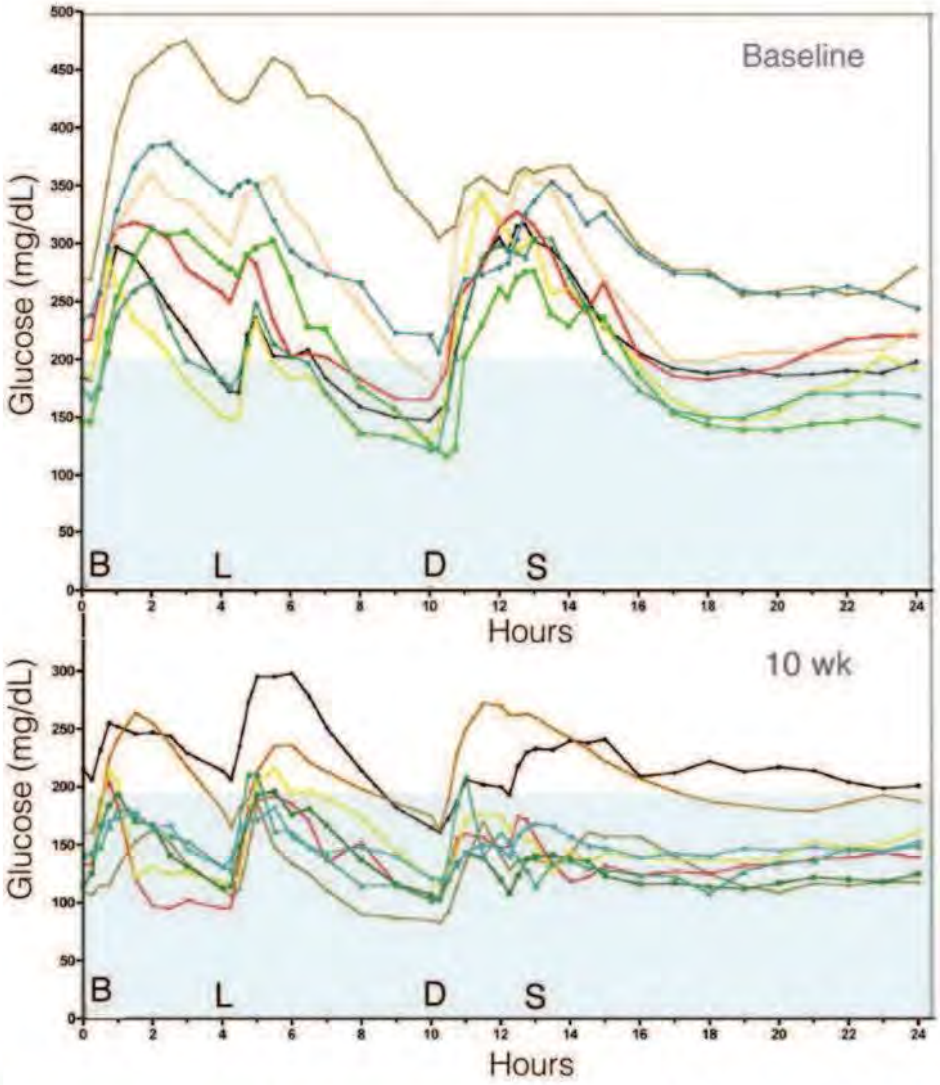

Fig. 3. Twenty-four h glucose responses at baseline and after at 10 wk on a weight-maintaining low-bioavailable glucose diet ($LoBAG_{30}$) for eight individuals. Time of ingestion of breakfast (B), lunch (L), dinner (D), and snack (S) as indicated. Redrawn from reference[9].

diet following Diabetes UK nutritional recommendations for 3 mo. Thirteen people with type 2 diabetes and 13 controls without diabetes were included. Weight loss was greater in the low-carbohydrate arm (6.9 versus 2.1 kg). Most important, the study reported individual responses, which are shown in Figure 4A. Almost all participants in the low-carbohydrate arm were successful at a loss of 2 kg as an arbitrary cutoff mark, whereas only about half of the healthy diet group reached this mark.

Figure 4B compares weight loss on a VLCKD compared with a low-fat diet. Three things are notable in this figure. First, weight loss is better on the VLCKD than the low-fat diet: Inspection of points along the x-axis shows that 70% of the low-fat individuals lost<8 kg (right side of vertical dotted line), whereas 80% of the VLCKD participants lost more than this amount, and along the y-axis, more than one-third of the low-fat individuals increased levels of glycated hemoglobin and only about 10% of the VLCKD did. Finally, as pointed out previously, again by inspection, there is little correlation between the two parameters.

Low-fat diets have in fact, shown very poor results, in the long term, for weight loss in nondiabetic individuals. The Womens Health Initiative (WHI) is the most recent example. In the study [24], diet performance in 48,000 postmenopausal women was compared with usual behavior. The low-fat intervention group was encouraged to consume a 20% fat diet, rich in fruits, vegetables, and grains. Modest weight loss (average 2.2 kg) occurred in the first year. By the end of the intervention, this weight had been regained. The authors made the very modest statement: A low-fat eating pattern does not result in weight *gain* in postmenopausal women. An editorial response to this study published in *JAMA*, stated: despite some successes, overall the low-fat dietary approach has been a failure with the US public, which is in desperate need of effective obesity treatment and prevention strategies [25]. The WHI was also distinguished by a failure to show any benefit in the prevention of diabetes or cardiovascular disease [24,26,27].

It should also be emphasized that popular implementations of low-carbohydrate diets like the Atkins diet [28,29] or Protein Power [30] put no formal limit on caloric consumption on the assumption that the greater satiety of protein and fat will provide control of intake. As a result, it has been traditional to carry out comparisons in which low-carbohydrate diets are ad libitum, whereas the control diets, usually low-fat, are explicitly

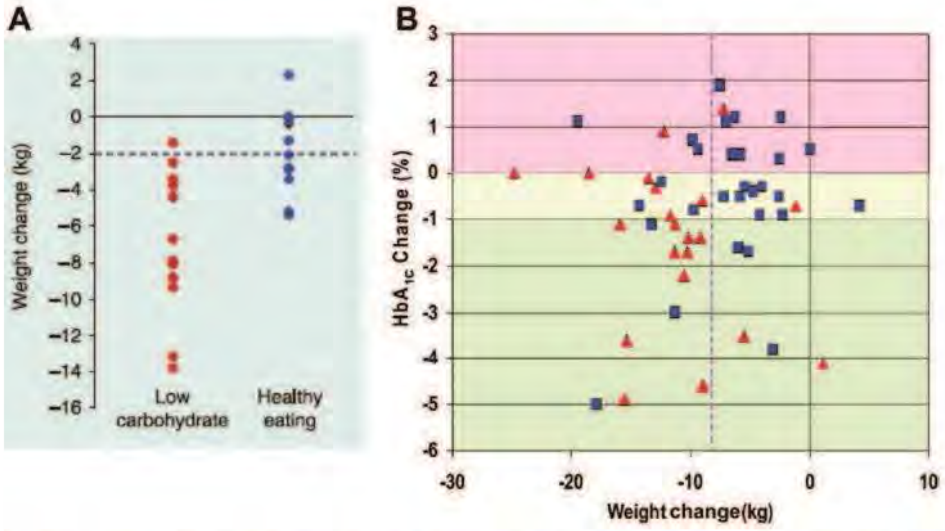

Fig. 4. Effect of diet on weight loss in people with type 2 diabetes. (A)Data from Dyson et al.[23]comparing a low-carbohydrate diet with the healthy-eating diet of the Diabetes UK agency. (B)Comparison of weight loss and changes in glycated hemoglobin. Very low-carbohydrate ketogenic diet (red triangles) is compared with a low-glycemic index diet (blue squares). Data from[6].

restricted in calories [31,32]. That the low-carbohydrate diets usually do better under these conditions supports the idea of implicit control of total intake and has to be considered a clear benefit for this approach to weight loss.

Point 5. Adherence to low-carbohydrate diets in people with type 2 diabetes is at least as good as adherence to any other dietary interventions and is frequently significantly better.

Adherence to low-carbohydrate diets, as formally measured in clinical trials, is usually equal to or better than other diets containing the same number of calories and is comparable with that for many pharmacologic interventions. A comparison of the number of completers of carbohydrate-restricted vs fat-restricted diets in 19 studies (Fig. 5) showed similar behaviors for the two regimes. If anything, adherence was better on the low-carbohydrate arms [33]. Comparable responses have been reported elsewhere [34]. Positive results are usually attributed to the effect of carbohydrate restriction on satiety and appetite suppression due to behavioral effects or hormones. In a study of The Active Low-Carber Forum, an online discussion group with >150,000 members, a common assertion was that a low-carbohydrate regimen provides the greatest degree of satisfaction [35]. Protein and fat are known to induce satiety and to reduce hunger-inducing blood sugar swings, likely via modulation of insulin-mediated and signaling pathways that send orexigenic signals to the brain. Additionally, patients who are on insulin or insulin secretagogues are able to reduce their doses on carbohydrate-restricted diets and find they are less likely to need to feed their insulin. As noted previously, in many studies, the low-carbohydrate group is allowed unlimited access to food as long as carbohydrate is reduced, whereas the low-fat control is explicitly constrained to reduction in calories, an obvious benefit for compliance. In this sense, compliance is tied to the features of the diet but encouragement by peers and health providers is a major factor.

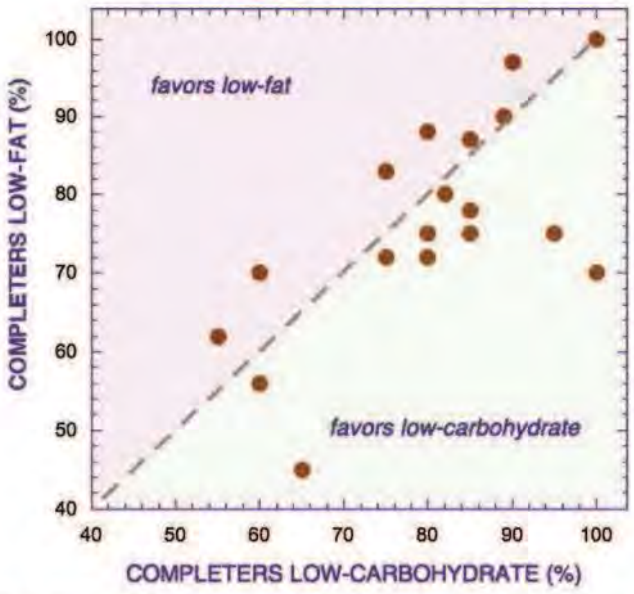

Fig. 5. Comparison of percent completion of diet studies. Each point represents a comparison from one of 19 studies. Low-carbohydrate values on the horizontal axis. Low-fat values on vertical axis. Data from[33]which contains references to individual studies.

Point 6. Replacement of carbohydrate with protein is generally beneficial

In practice, reduced-carbohydrate diets are not generally high-protein diets except in comparison with low levels recommended in high-carbohydrate diets. It is also generally recommended that carbohydrate is replaced by fat. However, a large number of RCTs have compared higher-protein, lower-carbohydrate diets (HPLCDs) with low-fat diets, and a number of systematic reviews and meta-analyses have assessed efficacy and short-term safety. These analyses have found that HPLCDs have a more favorable effect on weight loss, body composition, resting metabolic rate, and cardiovascular risk than fat-reduced diets. One meta-analysis included 23 RCTs involving 1141 obese nondiabetic participants who were reported in the literature to be on a low-carb diet, regardless of the actual diet

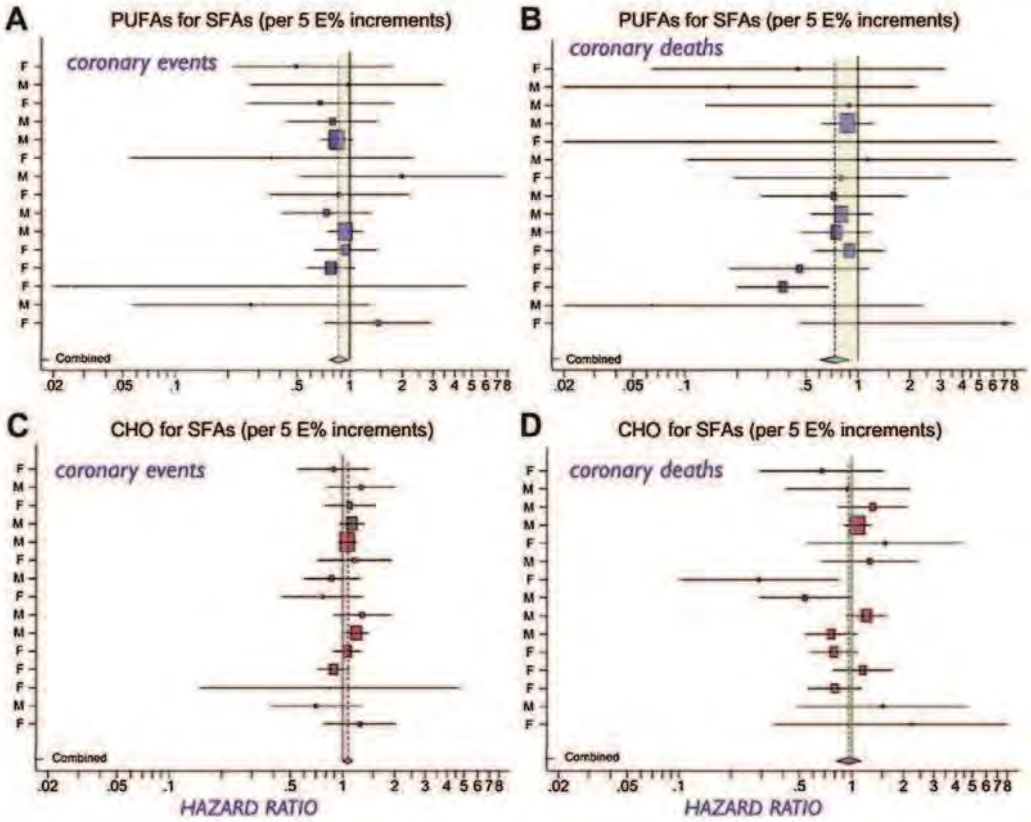

Fig. 6. Hazard ratios and 95% confidence intervals for coronary events and deaths in the different studies in a meta-analysis. Each line indicates a different cohort study with either men (M) or women (W). Individual studies are indicated in the original meta-analysis[53]. Red is increased risk by substitution for SFAs. Green indicates lower risk if SFA is substituted by indicated nutrient. Figure modified from[53]. Used with permission. CHO, carbohydrate; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid.

composition or degree of carbohydrate restriction [36]. Within-group changes, as opposed to comparisons with low-fat or other control diets, were measured. The lower carbohydrate diets were associated with significant decreases in body weight, body mass index, TG levels, and blood pressure; additionally, they showed improvement in several other metabolic and lipid indicators.

A meta-regression of RCTs was used to determine the comparative effects of protein and carbohydrate during energy restriction [37]. The study examined 87 trials with 165 intervention groups, comparing diets providing at least 1000 kcal/d (4200 kJ/d). Diets that provided <35% to 41% of energy from carbohydrate were associated with a 1.7 kg greater weight loss, a 0.7 kg greater loss of fat-free mass, and a 2 kg greater loss of fat mass than diets with a higher percentage of energy from carbohydrate. In studies lasting >12 wk, the effects were increased to 6.6 kg weight loss and 5.6 kg greater fat loss. Protein intakes >1.05 g/kg were associated with 0.60 kg additional fat-free mass retention compared with diets with protein intakes <1.05 g/kg. In studies with duration >12 wk, this difference increased to 1.2 kg. It has been concluded that HPLCDs favorably affect body mass and composition independent of energy intake which, in part, supports the proposed metabolic advantage of these diets [38,39].

Point 7. Dietary total and saturated fat do not correlate with risk for cardiovascular disease

Several large and expensive clinical studies have been carried out since the so-called diet heart hypothesis was framed in the middle of the 20th century [40,41]. From the original Framingham study [42]to the WHI [26], as well as more than a dozen additional studies, have failed to show an association between dietary lipids and risk for cardiovascular disease (CVD). There is now a large volume of literature of both scientific papers [43–47] and popular books [48–51] documenting the failure of attempts to support the diet heart hypothesis. Few rebuttals have been offered [52]. The very strong recommendations from health agencies predicted that none of these trials should fail. In fact, almost all of them have failed.

Three additional recent meta-analyses should help settle the question of a causal link between dietary lipid and CVD [53–55]. Follow-up results were pooled from 11 major cohort studies that followed the replacement of saturated fatty acids (SFAs) with either polyunsaturated fatty acids (PUFA; Fig. 6A, B) or carbohydrate [53].

The effect of replacing 5% of energy intake from SFA is shown inFigure 6 [53]. Conclusions from the individual primary studies are compelling. Almost all of the studies show no effect of replacement of SFA with either carbohydrate or PUFA. The statistical rule is that if the 95% confidence interval (CI) crosses 1, there is no difference. The shaded areas in Figure 6, meant to represent the differences between the pooled data, are very small. More important, in our view, the statistical analysis is inappropriate. Meta-analyses are appropriate for small underpowered studies where there is a chance that combining them may point to some unappreciated correlation. Figure 6, however, collates large-scale, well-controlled studies that individually showed no effect. It is questionable whether any statistical method will allow one to average studies that have not shown a statistical association and come up with a meaningful correlation.

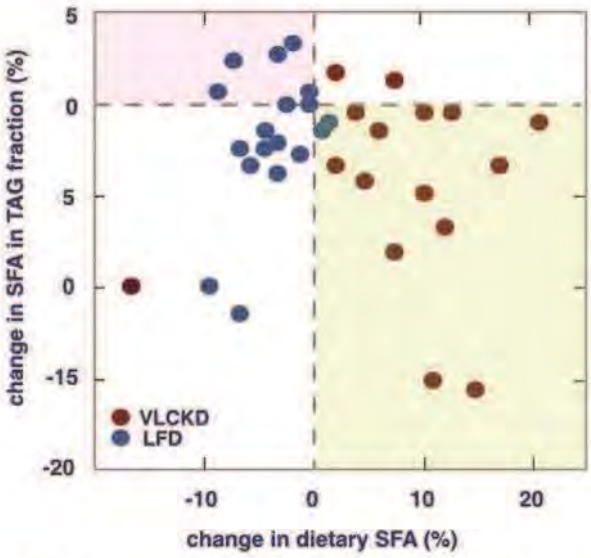

Fig. 7. Lack of association between dietary and plasma TG SFAs. In the green area, an increase in dietary SFA is associated with a reduction in SFA in the TG fraction in plasma. In the pink area, SFA increases even though dietary SFA is reduced. Data from[61]. LFD, low-fat diet; SFA, saturated fatty acid; TG, triglyceride; VLCKD, very low-carbohydrate ketogenic diet.

Even taking previous conclusions [53] at face value, the calculated hazard ratios increased when SFAs were replaced with carbohydrate and the study reported a modest significant direct association between carbohydrates and coronary events. A similar analysis concluded that replacing SFA with CHO [carbohydrate] has no benefits [54], and others similarly concluded, A meta-analysis of prospective epidemiologic studies showed that there is no significant evidence for concluding that dietary saturated fat is associated with an increased risk of CHD or CVD [43,44]

In the end, the fact that so few individual studies found any effect is what is striking. None of the 15 studies on replacing saturated fat with carbohydrate showed any effect on coronary events and only two found a statistical effect on coronary deaths. Indeed, one of the few studies widely quoted as showing an effect of SFA is the Finnish Mental Hospital Study whose scientific limitations have been extensively analyzed [56], including the observation that many changes could be attributed to differences in antipsychotic medications. Looking at the studies in Jakobsen's analysis (Fig. 6), and the fact that some of these studies date from >20 y ago, it seems reasonable to conclude that if there is any risk in replacing carbohydrate with SFAs, it is still conjectural and long term and should not override the established and immediate benefit of the replacement.

Point 8. Plasma saturated fatty acids are controlled by dietary carbohydrate more than by dietary lipids

Despite the failure to establish real risk in point 8, a significant barrier to implementation of carbohydrate restriction as a therapy in diabetes remains the traditional fear of the effect on blood lipids and, for example, the tendency of dietary SFA to raise blood total cholesterol [52,57]. The rationale for this concern followed from the idea that because dietary SFA raised cholesterol and plasma cholesterol was correlated with CVD [58], it was assumed that dietary SFA would cause heart disease. The fallacy is that the data were statistical and, to show cause, one had to show that the people whose cholesterol was raised by SFA were the same people whose cholesterol predicted CVD. In other words, it is necessary to show a direct effect of dietary SFA on CVD. The previous point emphasized that this has been impossible to do. Dietary SFA does not correlate with CVD. On the other hand, it is increasingly understood that plasma SFAs are associated with increased risk for CVD and insulin resistance [59]. in humans, plasma SFAs do not correlate with dietary saturated fat but, rather, are more dependent on dietary carbohydrates [5,60–62]. Elevated SFAs arise from increased production of TG-containing lipoproteins, reduced clearance, and the effect of dietary carbohydrate on de novo fatty acid synthesis. In one study 40 patients diagnosed with metabolic syndrome were treated with either a low-fat diet or a VLCKD. The VLCKD group showed reduced plasma SFA levels compared with the low-fat group, despite having consumed a threefold higher intake of dietary saturated fat compared with the low-fat group. Figure 7 shows that a low-carbohydrate diet was more likely to reduce SFA in plasma TG fraction than a low-fat diet. It should be mentioned, however, that an increase in dietary saturated fat is not a necessary feature of a carbohydrate-restricted diet.

A further ambiguity in the literature arises from extrapolation of rodent data. In some mouse models, dietary saturated fat is correlated with plasma saturated fat but this result is not seen in

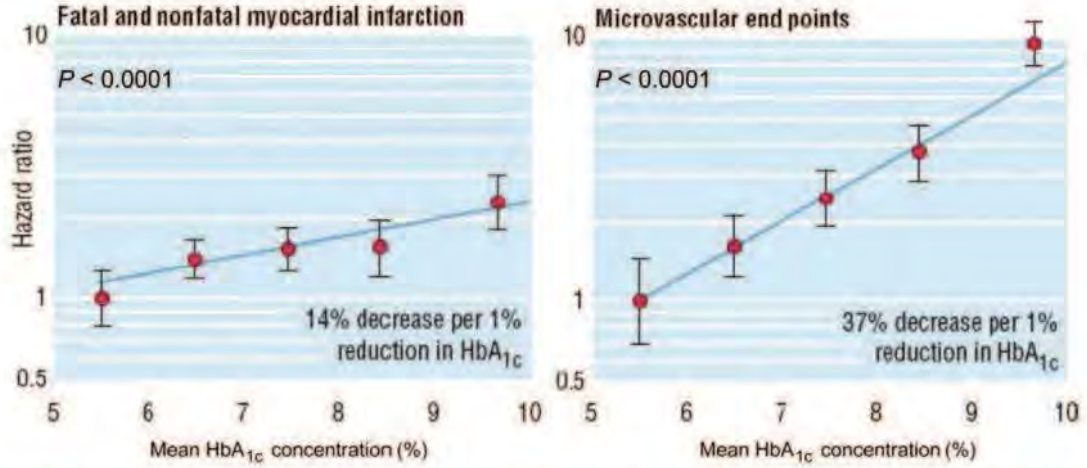

Fig. 8. Dependence of risk for myocardial infarction and microvascular end points on hemoglobin A_{1c}. Data adjusted for age at diagnosis of diabetes, sex, ethnic group, smoking, presence of albuminuria, systolic blood pressure, high- and low-density lipoprotein cholesterol, and triglycerides. Modified from[65–67]. Used with permission. Hemoglobin (Hb).

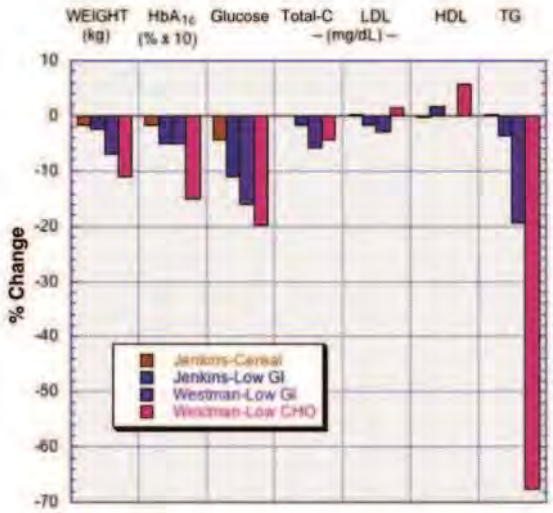

Fig. 9. Comparison of low-glycemic index diet with high-cereal diet, and of low-glycemic index diet with low-carbohydrate diet. Data from[6,70]. Redrawn from [75]. CHO, carbohydrate; GI, glycemic index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; Total-C, total cholesterol.

humans [63]. Some, although not all, studies in rodents consistently show negative effects of high-fat diets on obesity and insulin resistance, in some cases, even in the absence of carbohydrate [64]. These outcomes are not seen in humans and one should be circumspect about generalizing results to a human population. Among other species differences, some common mouse lines are more resistant to nutritional ketosis.

Point 9. The best predictor of microvascular and, to a lesser extent, macrovascular complications in patients with type 2 diabetes, is glycemic control (HbA_{1c})

The results in point 7, that dietary SFA does not correlate with CVD, did not specifically include individuals with diabetes. It is known that patients with both type 1 and type 2 diabetes are at increased risk for CVD. The United Kingdom Prospective Diabetes Study (UKPDS), described next, addresses the question of the relation between diabetes and CVD.

The UKPDS studied the incidence of macrovascular or macrovascular complications in a population of 5102 patients with newly diagnosed type 2 diabetes in 23 centers in the United Kingdom between 1977 and 1991 [65–67]. The study found that the key controlling variable was HbA_{1c}. As HbA_{1c} increased, there was a corresponding increase in fatal and nonfatal myocardial infarction (MI) events. There was a 14% decrease in MI for every 1% reduction in HbA_{1c}. The right panel in Figure 8 shows results for microvascular end points. There was a dramatic 37% decrease in these end points for microvascular risk for each 1% reduction in HbA_{1c}. It is important to consider that the authors found that no specific thresholds of glycemia were found. Risk appeared to increase for any HbA_{1c} above normal, taken in this study as 6%. Other studies had similarly failed to identify any threshold effect of plasma glucose effects on cardiovascular outcome [68]. The results are critical as a clear demonstration that the increased risk for CVD in people with diabetes is the diabetes itself as indicated by HbA_{1c}. Point 1 emphasized that HbA_{1c} is reliably reduced by low-carbohydrate diets. The alternative, cited by the authors, of adding insulin to improve the relatively modest reduction in glycaemia achieved with oral hypoglycaemic treatments can be constrained by reluctance from patients and providers because, in part, of side effects such as weight gain.

Point 10. Dietary carbohydrate restriction is the most effective method (other than starvation) of reducing serum TGs and increasing high-density lipoprotein

Carbohydrate restriction is the single most effective intervention for reducing all of the features of metabolic syndrome [5,62,69].Figure 9 shows the results from a study comparing a low glycemic index (low-GI diet) with a standard high-cereal diet in 210 people with type 2 diabetes [70]. Results show a 1.7 mg/dL increase in high-density lipoprotein (HDL) levels for the low-GI diet compared with a 0.2 mg/dL decrease for the high-cereal diet. Coincidentally, at almost the same time, another study [6]carried out a comparison, under very similar conditions, of a low-GI diet with a VLCKD (<20 g/d carbohydrate). The difference in outcomes between these two groups is striking. Figure 9 shows the results of a study in 84 obese type 2 diabetics in comparison with the results from a high-cereal/low-GI study that stands as the single most telling indication of the potential for carbohydrate restriction in diabetes. The low-carbohydrate diet (reddish bar) shows the greatest decrease in TG, as well as decrease in weight, HbA_{1c} and glucose and a greater increase in HDL.

Total and/or LDL cholesterol are the most commonly assessed lipid markers for CVD risk despite the general recognition that they are not good predictors. Several other parameters have been shown to provide stronger evidence of risk and these tend to be reliably improved by dietary carbohydrate restriction. These include apolipoprotein (apo) B [71], ratio of total cholesterol to HDL, higher populations of the smaller dense LDL known as pattern B [72,73], as well as the ratio of apoB to apoA1. The ratio of TG to HDL, which is also improved more by carbohydrate restriction is taken as a correlate of the smaller dense LDL, which is not routinely measured [74].

Despite their routine measurement, a number of studies have failed to support any connection between LDL cholesterol lowering and improved mortality. During thefirst 14 y of the Framingham study, for every 1 mg/dL per year drop in cholesterol levels there was a 14% increase in cardiovascular death and an 11% increase in overall mortality [68]. Similar increase in mortality following a drop in cholesterol was seen in other studies [76,77].

In our view, Figure 9 in combination with Figure 3 tells the whole story on dietary interventions in type 2 diabetes. The important point is that there is nothing in these studies that suggests that there is any long-term harm as long as the protocol is followed. One cannot start from the possibility of risk. In short-term comparisons, it is the diet that does poorly that is of concern in the long run. As in point 5, adherence is at least as good on a low-carbohydrate regimen as any other dietary protocol or even some pharmacologic interventions. Common sense dictates that the two most important factors in adherence are efficacy—people will stay on a diet that works—and encouragement from the health provider. The first of these is a feature of the diet. The second, again, is up to the health provider.

Point 11. Patients with type 2 diabetes on carbohydrate-restricted diets reduce and frequently eliminate medication. People with type 1 usually require lower insulin

Dietary carbohydrate restriction, because of its increased effectiveness in glycemic control, frequently leads to reduction and often complete elimination of medication in type 2 diabetes.

Similarly, patients with type 1 typically require less medication on low-carbohydrate diets [78,79]. In both cases, carbohydrate restriction reduces the number and severity of hyperglycemic and hypoglycemic episodes. For people with type 1 diabetes, decreasing the amount of carbohydrates in a meal reduces error in determining insulin needs to match it.

Reduction of medication concomitant with reduction in symptoms is considered a sign of efficacy in most therapeutic contexts. Table 2 shows results from a study that demonstrated reductions in medication in patients on a VLCKD (20 50 g/d carbohydrate) compared with a moderate carbohydrate diet that was explicitly lower in calories [80]. In the study, of 11 patients on medication in the VLCKD arm who finished the study, 5 reduced or discontinued one medication and 2 discontinued all medications. Of the 13 patients on the moderate carbohydrate diet, only 1 discontinued a sole medication. Similarly, another study found that 17 of 21 patients with type 2 diabetes reduced or discontinued diabetes medication upon carbohydrate restriction [81]. This result is a general feature of carbohydrate restriction in type 2 diabetes [82 84].

Point 12. Intensive glucose lowering by dietary carbohydrate restriction has no side effects comparable to the effects of intensive pharmacologic treatment

The ACCORD (Action to Control Cardiovascular Disease in Diabetes) trial was halted because of deaths from CVD [85]. After 3.5 y of follow-up, there were 257 deaths in the intensive-therapy group compared with 203 in the standard-therapy group (hazard ratio, 1.22; 95% CI, 1.01 1.46; P=0.04). Hypoglycemia requiring assistance and weight gain >10 kg were more frequent in the intensive-therapy group (P<0.001). The results were interpreted as showing a previously unrecognized harm of intensive glucose lowering in high-risk patients with type 2 diabetes. Results were reported as such in the popular media. Logically, however, it is not the target but the method of trying to attain it. Intensive use of medications in high-risk patients is a more reasonable explanation. There are numerous concerns about diabetes medications [85].

That the goal of lowering blood glucose has no inherent harm to offset benefit can be seen in the data for a subset of participants in the ACCORD trial who had lower HbA_{1c} values (Table 3). These patients did not show the same risk as those with higher values.

Risks from several medications prescribed for diabetes have been identified. Rosiglitazone is the subject of continuing debate. It has been suggested that the agent posed a significant risk for MI and a risk for death from CVD, the latter of borderline significance. The original result has been disputed [86 89]and the fate of the drug is unknown, but no such ambiguity attaches to dietary carbohydrate restriction.

Discussion

The need for a reappraisal of dietary recommendations stems from the following:

1. General failure to halt the epidemic of diabetes under current guidelines.
2. The specific failure of low-fat diets to improve obesity, cardiovascular risk, or general health (points 1 and 4).
3. Constant reports of side effects of commonly prescribed diabetic medications, some quite serious (points 12).
4. Most importantly, the continued success of low-carbohydrate diets to meet the challenges of improvement in the features of diabetes and metabolic syndrome in the absence of side effects.

Table 2
Comparison of Effects of Diet on Medication Use at Baseline and at 3 mo Among Participants Assigned to Either of the Indicated Diets*

Low-carbohydrate ketogenic diet (not calorie restricted)		
1	Glimepiride, Actos, Exenatide, Metformin	Dropped out of study
2	Metformin 500 mg bid	No change
3	Metformin 850 mg bid	No change
4	Metformin 1000 mg bid	No change
5	Metformin 2000 mg	No change
6	Metformin 500 mg	Metformin discontinued
7	Glyburide 2.5 mg bid, Metformin 1000 mg bid	Glyburide and metformin discontinued
8	Glipizide 2.5 mg, Metformin 1000 mg bid	Glipizide discontinued
9	Glipizide 5 mg, Metformin 1000 mg bid	Glipizide discontinued
10	Glyburide 2.5 mg bid, Metformin 500 mg	Glyburide discontinued
11	Januvia 50 mg, Metformin 1000 mg bid	Januvia discontinued
12	Glyburide 2.5 mg, Januvia 100 mg, Metformin 1000 mg bid	Glyburide and januvia discontinued
Moderate-carbohydrate calorie restricted		
1	Metformin 500 mg	No change
2	Metformin 500 mg	No change
3	Metformin 500 mg bid	No change
4	Metformin 500 mg bid	No change
5	Metformin 500 mg bid	No change
6	Metformin 1000 mg bid	No change
7	Metformin 1000 mg bid	No change
8	Glipizide 10 mg, metformin 1000 mg bid	No change
9	Glimepiride 8 mg, januvia 1000 mg bid, metformin 50 mg bid	No change
10	Glipizide 2.5 mg bid, metformin 1000 mg bid	No change
11	Glipizide 5 mg, Metformin 2000 mg, Januvia 50 mg	No change
12	Metformin 850 mg tid	Metformin lowered to 500 mg bid
13	Glipizide 5 mg, Metformin 500 mg bid, Acarbose 50 mg tid	Glipizide discontinued

* Data from [80].

The benefits of carbohydrate restriction are immediate and well documented. Concerns about the efficacy and safety of carbohydrate restriction are long term and conjectural rather than data driven. Most objections stem from the proposed dangers of total or saturated fat embodied in the so-called diet heart hypothesis. At this point, the diet heart hypothesis has had a record of very limited clinical or experimental success to support its position. The issue has become the subject of strong reaction in both the scientific literature and the popular press [48,50,51,90] (point 8).

It is well established that weight loss, by any method, is beneficial for individuals with diabetes. The advantages to a low-carbohydrate approach are that, because of greater satiety,

Table 3
Difference in Event Incidence (%) Hazard Ratio for Subsets of Patients in the ACCORD Trial with Lower HbA_{1c} Values or Who Had Not Had a Previous Event (grey highlight)*

	Event incidence (%)	HR	Statistically significant
Previous cardiac event			
Yes	10.9	1.1	No
No	5	0.8	Yes
Baseline HbA_{1c}			
≤8%	5.8	0.7	Yes
>8%	8.3%	1.05	No

ACCORD, Action to Control Cardiovascular Disease in Diabetes; Hb, hemoglobin; HR, hazard ratio

* Data from reference [85].

explicit calorie reduction on the part of the patient may not be required. There may be de facto reduction in calories without the need for replacement. The extent to which there is replacement, either fat or protein may be beneficial (points 4 and 6) although, in practice, fat is recommended unless there is already lower protein. Concerns about high protein in carbohydrate restriction have been raised but, except for those people with existing kidney disease, none has ever been demonstrated [91]. Protein also tends to a stable self-limiting part of the diet. Perhaps most important, if carbohydrate is low, glycemic control and other physiologic parameters are improved even if weight loss is not accomplished (point 3).

Finally, it should be recognized that the use of low-carbohydrate diets is not a recent experiment and may well approximate the diet used by much of humanity for tens of thousands of years before the rise of agriculture. Current knowledge dictates that carbohydrate restriction should be a default treatment for type 2 diabetes and a default adjunct therapy for type 1. Given the superior outcomes of carbohydrate-restricted diets, patients should not be discouraged from adhering to them as is frequently observed. They should, in fact, be encouraged to follow this approach.

The 12 points of evidence represent the best investigated and least conjectural ideas on diabetes. It is unlikely that one dietary strategy, any more than one kind of pharmacologic treatment will be best for all individuals. Patients can refuse medication or opt out of surgery, but they cannot *not* be on a diet and low-carbohydrate is the reasonable place to start. We recognize that there are many complications and issues that are still not understood, however, we have tried to isolate the factors that have the fewest contradictions.

This review emphasized the most obvious principles. An anonymous reviewer, however, raised two important if more conjectural points. We were asked To specify role of starch versus mono- and disaccharides in carbohydrate-semi-restricted diet (optimal proportions). and In discussion to draw more attention to the possible disadvantages of low-carbohydrate diet in people with diabetes.

Role of starch versus mono- and disaccharides

Replacement of carbohydrate with fat or, in some cases, with protein, is beneficial in both types of diabetes leading to better glycemic control, weight loss, cardiovascular risk markers, and reduction in medication. This is what we know. That is what is established in well-controlled experiments in individuals with diabetes (points 1, 3, and 10). The evidence does not contain strong data on which carbohydrates should be removed (or even what the effect of different fats of protein might be). On first principle, glucose is of greatest importance in diabetes. The sudden interest in fructose and sucrose as unique types of carbohydrate has made the discussion quite controversial. Both the scientific [92,93] and popular literature [94] have been unrestrained in attributing harm to fructose. Generally, fructose is known to have unique effects compared with glucose, although most of these are seen on a high-carbohydrate diet [95] and there may be little difference as carbohydrate is lowered. It is likely that on a low-carbohydrate diet, most fructose that is consumed will be converted to glucose. We have provided a perspective on the metabolism of fructose [96] where we emphasize its integration into general carbohydrate metabolism. The fact that up to 60% of ingested fructose can be converted to glucose makes the analysis of which sugar does what very difficult.

The definitive experiment, testing whether removing fructose is preferable to removing glucose in the implementation of a low-carbohydrate diet has never been performed. This is presumably due to the poor acceptance of low-carbohydrate diets in general[4]. One study showed that glycemic response was lower after ingestion of a low-starch meal with 43% total carbohydrate and high levels of fruit compared with a high-starch, high-carbohydrate meal or a 40% carbohydrate typical American meal [97]. There was also, as expected, a lower 24-h integrated serum insulin response. The results demonstrate the value of specifically removing starch, although it was not determined whether removing sugar would be equally effective or better. As above, this group has also shown good results simply by reducing glucose (point 3).

Because of the limited insulin effect, it was once thought that fructose might be an acceptable source of carbohydrate, but this turned out to be questionable and may actually have a deleterious effects if administered intravenously alone. Analysis of the hepatic metabolism shows that the liver expects the two sugars to appear together [96], fructose (e.g., increases glucokinase activity).

The reviewers original question is framed in terms of carbohydrate-semi-restricted diet (optimal proportions). It is unlikely that there is a general answer. As a guide for the patient with diabetes, the prescription of many agencies to eat to the meter seems like a good one.

Possible disadvantages of low-carbohydrate diet in people with diabetes

To assess the disadvantages of carbohydrate restriction for individuals with diabetes, one has to ask what the standard is and where it came from. The idea that there is an effective diet of known macronutrient composition, one tested in long-term, or even short-term trials, that is beneficial in treating diabetes is implied by the question. To our knowledge, no such diet exists. The more dietary carbohydrate, the more medication will be required (point 11). The disadvantage to a low-carbohydrate diet, as in any intervention, will rest with individual choices. Low-carbohydrate diets generally have better compliance (point 5) but individuals vary in tastes and assessment of risk benefit perceptions.

The flipside of the benefit from reduced medication (point 11) presents a real potential disadvantage. Because of the effectiveness of carbohydrate restriction on glycemic control, there is a danger of hypoglycemia for those patients on glucose-lowering medication. It is recommended that medication be reduced in advance of initiating a low-carbohydrate diet. Personal communications suggest that there are a variety of strategies for reducing insulin or other drugs. Whether the patient (or the physician) knows this is potentially serious question. Instructions for the study in reference [80], for example, provide the following guide:

Metformin was continued for the duration of the study unless the participant or his/her doctor requested it be lowered, at which point the dose was cut in half or discontinued completely. Sulfonylurea doses were reduced in half if the entry HbA1c was <7.5% or discontinued if the participant was on a minimum dose. Sulfonylurea was discontinued if predinner glucose levels went below 110 mg/dL despite prior dose reduction; thiazolidinediones were continued for participants with starting with a HbA1 c above 7% and discontinued for those with starting HbA1 c below 7%.

Conclusion and recommendations

What evidence would be required to change the current recommendations for dietary treatment in diabetes? Evidence-based medicine tends to emphasize RCTs as a gold standard. Such absolute requirements, however, are unknown in any scientific discipline. As in a court of law, science admits whatever evidence is relevant [98]. Following the legal analogy, one has to ask: Who decides on the admissibility of the evidence? The parody by Smith and Pell [99]has been described as both funny and profound in illustrating how there is not a single type of experiment that fits every scientific question. Given the current state of research funding and the palpable bias against low-carbohydrate approaches [4], it is unlikely that an RCT can be performed that will satisfy everybody. The seriousness of diabetes suggests that we have enough evidence of different types to reevaluate our current recommendations for treatment.

This review has described 12 points of evidence based on published clinical and experimental studies and the experience of the authors. The points are supported by established principles in biochemistry and physiology and emphasize that the benefits are immediate and documented while the concerns about risk are conjectural and long term.

We would recommend that government or private health agencies hold open hearings on these issues in which researchers in carbohydrate restriction can make their case. We think that traditional features of the analysis of evidence such as vigorous cross-examination should be part of the process. We suggest that open discussion with all sides contributing will be valuable. The seriousness of diabetes suggests that a bench decree will be inappropriate.

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