



# The Effects of a Mediterranean Diet on the Need for Diabetes Drugs and Remission of Newly Diagnosed Type 2 Diabetes: Follow-up of a Randomized Trial

*Diabetes Care* 2014;37:1824–1830 | DOI: 10.2337/dc13-2899

Katherine Esposito,<sup>1</sup> Maria Ida Maiorino,<sup>1</sup>  
Michela Petrizzo,<sup>1</sup> Giuseppe Bellastella,<sup>2</sup>  
and Dario Giugliano<sup>2</sup>

## OBJECTIVE

To assess the long-term effects of dietary interventions on glycemic control, need for diabetes medications, and remission of type 2 diabetes.

## RESEARCH DESIGN AND METHODS

Originally, in a two-arm trial design, overweight, middle-aged men and women with newly diagnosed type 2 diabetes were randomized to a low-carbohydrate Mediterranean diet (LCMD;  $n = 108$ ) or a low-fat diet ( $n = 107$ ). After 4 years, participants who were still free of diabetes medications were further followed up until the primary end point (need of a diabetic drug); remission of diabetes (partial or complete) and changes in weight, glycemic control, and cardiovascular risk factors were also evaluated.

## RESULTS

The primary end point was reached in all participants after a total follow-up of 6.1 years in the low-fat group and 8.1 years in the LCMD group; median survival time was 2.8 years (95% CI 2.4–3.2) and 4.8 years (4.3–5.2), respectively. The unadjusted hazard ratio for the overall follow-up was 0.68 (0.50–0.89;  $P < 0.001$ ). LCMD participants were more likely to experience any remission (partial or complete), with a prevalence of 14.7% (13.0–16.5%) during the first year and 5.0% (4.4–5.6%) during year 6 compared with 4.1% (3.1–5.0%) at year 1 and 0% at year 6 in the low-fat diet group.

## CONCLUSIONS

In patients with newly diagnosed type 2 diabetes, an LCMD resulted in a greater reduction of HbA<sub>1c</sub> levels, higher rate of diabetes remission, and delayed need for diabetes medication compared with a low-fat diet.

Type 2 diabetes is now pandemic and shows no signs of abatement. The estimated worldwide prevalence of diabetes among adults aged 20–79 years was 366 million (8.3%) in 2011, and this value is predicted to rise to ~562 million (9.9%) by 2030 (1). This increase in type 2 diabetes is inextricably linked to changes toward a Western lifestyle (high-energy diets with reduced physical activity) in developing countries and the rise in the prevalence of overweight and obesity (2). Nutritional epidemiology has established the associations of overall dietary patterns with diabetes risk

<sup>1</sup>Diabetes Unit, University Hospital at the Second University of Naples, Naples, Italy

<sup>2</sup>Division of Endocrinology and Metabolic Diseases, University Hospital at the Second University of Naples, Naples, Italy

Corresponding author: Katherine Esposito, [katherine.esposito@unina2.it](mailto:katherine.esposito@unina2.it).

Received 11 December 2013 and accepted 20 February 2014.

Clinical trial reg. no. NCT00725257, [clinicaltrials.gov](http://clinicaltrials.gov).

This article contains Supplementary Data online at <http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc13-2899/-/DC1>.

© 2014 by the American Diabetes Association. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

(3) and with intermediate outcomes such as weight gain, increased blood pressure, and insulin resistance and hyperglycemia (4,5).

Mediterranean-style diets (Med diets) with a high proportion of monounsaturated fat provide cardiovascular benefits and increase insulin sensitivity (6,7); the American Diabetes Association (ADA) recommends low-carbohydrate, low-fat calorie-restricted, or Med diets for weight loss in overweight and obese patients who have or are at risk for type 2 diabetes (8). The results of large controlled trials show that an intensive lifestyle intervention focusing on weight loss did not reduce the rate of cardiovascular events in overweight or obese adults with type 2 diabetes (9), while a Med diet reduced the incidence of major cardiovascular events in adults at high cardiovascular risk, including type 2 diabetic patients (10). Consistent with the state of U.S. health, 1990–2010 (11), the aggregate of the 14 subcomponents of diet may be more important factors associated with disease burden than either physical inactivity or high BMI.

In a previous intervention trial (12), patients with newly diagnosed type 2 diabetes who were assigned to a low-carbohydrate Med diet (LCMD) were less likely to need oral therapy for hyperglycemia than patients assigned to a low-fat diet. The extended postcore follow-up of the study was designed to assess the long-term results of dietary interventions and also to determine their association with frequency of partial and complete remission of type 2 diabetes.

## RESEARCH DESIGN AND METHODS

The study was a randomized controlled trial aimed at prevention of antihyperglycemic drug therapy in type 2 diabetes by dietary intervention. The two-arm trial design of the study has been described previously (12). The study protocol was approved by the ethics committee, and all study participants gave written informed consent. Randomization started in 2004, and the trial was completed after a follow-up of 4 years. Subsequently, we decided to continue to monitor the participants who did not reach the primary end point. This report consists of the data obtained until 30 September 2012 (i.e., when the last patient reached the

primary end point), with a total follow-up of 8.1 years.

### Participants

Originally, 215 men and women with newly diagnosed type 2 diabetes were randomized (simple randomization) at the baseline visit to one of two treatment modalities, an LCMD group ( $n = 108$ ; proportion of women, 50%) or a low-fat diet group ( $n = 107$ ; proportion of women, 51.5%). Overweight (mean BMI  $29.6 \text{ kg/m}^2$ ), middle-aged (mean age 52.2 years) type 2 diabetic patients by ADA criteria (8), who had never been treated with diabetes medications, were eligible for the study. Mean fasting plasma glucose at baseline was  $160 \text{ mg/dL}$  (SD 32), and mean  $\text{HbA}_{1c}$  was 7.7% (0.9) ( $61 \text{ mmol/mol}$  [SD 5.6]), without significant differences between the two groups. The overall proportion of participants who were lost to follow-up was 9.25% in the Med diet group and 9.3% in the low-fat group (Supplementary Fig. 1).

### Intervention

The main goals of the dietary interventions were restriction of energy intake to 1,500 kcal/day for women and 1,800 kcal/day for men in both groups. The LCMD was rich in vegetables and whole grains and low in red meat, which was replaced with poultry and fish, with the goal of no more than 50% of calories from carbohydrates and no less than 30% calories from fat, with the main source of added fat 30–50 g of olive oil. The low-fat diet was rich in whole grains and restricted additional fats, sweets, and high-fat snacks, with the goal of no more than 30% of calories from fat and no more than 10% of calories from saturated fat.

Participants in both groups were given detailed dietary advice by nutritionists and dietitians to achieve the dietary goals in monthly sessions in the first year and bimonthly sessions thereafter. Participants were also instructed how to record their intake using food models and actual weights or amounts in terms of common measures. Adherence to the diets was assessed by session attendance and review of the diet diaries. Participants in both groups were also advised to increase their level of physical activity, with programs tailored on the basis of the results of a baseline

physical fitness test and safety concerns: gradual progression toward a goal of 175 min of moderate-intensity physical activity per week. All participants recorded occupational, household, and leisure time physical activity.

### Postcore Follow-up

All individuals who participated in the core intervention were invited to take part in the postcore follow-up. During this follow-up, all study participants had six monthly sessions with the study personnel (doctors, nurses, and dietitians). The coordinator of the study (K.E.) was the same during the course of postcore follow-up, with the same applying to the majority of diet operators. The visits included the same procedures as during the core intervention and were similar for all participants. Specific diet or exercise counseling was provided.

### Procedures and Measurements

At scheduled visits, staff members who were unaware of study-group assignments queried patients about all medical events and hospitalizations and measured weight, waist circumference, and blood pressure, along with assessing medication use and obtaining blood for analysis at the hospital laboratory. Hospital and other records were reviewed for potential cardiovascular events, with adjudication according to standard criteria.

All study participants completed a 3-day food record with a picture booklet of portion sizes of typical foods. The average intakes of total energy, total, saturated, monounsaturated, and polyunsaturated fat (proportion of the total daily energy intake), carbohydrates, and protein were calculated. For the ascertainment of physical activity status, we used the International Physical Activity Questionnaire (13) as an index of weekly energy expenditure using frequency (times per week), duration (in minutes of time), and intensity of sports or other habits related to physical activity. The parameters measured every 6 months included  $\text{HbA}_{1c}$  (high-pressure liquid chromatography traceable to the Diabetes Control and Complications Trial reference method), anthropometrics (weight and waist circumference), lipids (total and HDL cholesterol, and triglycerides), insulin, and adiponectin. All measurements

were made in the hospital's chemistry laboratory.

The primary outcome measure was time to introduction of diabetes medications. We also used HbA<sub>1c</sub> levels >7% (53 mmol/mol) as the primary outcome to test the possibility that investigators who were not blinded to treatment assignment might have made biased decisions to initiate or withhold drug therapy. As suggested by the ADA for clinical evaluation and management of diabetic patients (8), we measured HbA<sub>1c</sub> at baseline and every 3 months thereafter. Participants who had an HbA<sub>1c</sub> level >7% (53 mmol/mol) were given an additional 3 months to reinforce dietary guidance and physical activity; if the HbA<sub>1c</sub> level remained >7% (53 mmol/mol), the participant reached the primary end point, and the data were censored.

For remission analyses, diabetes was defined as having a fasting plasma glucose level of at least 126 mg/dL or HbA<sub>1c</sub> of at least 6.5% (48 mmol/mol). Partial remission of diabetes was defined as a transition from meeting diabetes criteria to a prediabetes level of glycemia (i.e., fasting plasma glucose level of 100–126 mg/dL and HbA<sub>1c</sub> of 5.7–6.5% [39–48 mmol/mol]); complete remission was defined as transition from diabetes criteria to full normalization of glucose (fasting plasma glucose level <100 mg/dL and HbA<sub>1c</sub> <5.7% [39 mmol/mol]).

Secondary outcome measures were changes in weight, coronary risk factors (lipid levels and blood pressure), and meeting ADA coronary risk factor goals (HbA<sub>1c</sub> level <7% [53 mmol/mol], blood pressure <140/80 mmHg, and LDL cholesterol level <100 mg/dL). Initially, the goal for blood pressure was set at <130/80 mmHg and then reset at <140/80 mmHg according to the new recommendations from the ADA (8).

### Statistical Analysis

We analyzed the data by intention-to-treat. Kaplan-Meier survival curves were calculated to estimate the probability of remaining free of diabetes medications in the two groups, with a two-sided log-rank test for comparisons. Participants who were lost during follow-up were treated as censored observations. We continued postcore follow-up until the last patient in each group reached the primary end point. We performed Cox regression for time

to introduction of diabetes medication, first using treatment value as the only dependent variable, then adding weight loss as an additional covariate (in categories of 1–2.5, 2.6–5.0, and 5 kg) to assess the effect of the dietary interventions independent of weight loss. We verified the underlying assumption of proportional hazards for the Cox regression models by demonstrating no statistically significant interaction between treatment and the log of the follow-up time ( $P = 0.83$ ). We performed the same analysis using HbA<sub>1c</sub> level >7% (53 mmol/mol) as the primary outcome. We compared the yearly prevalence of any remission (partial or complete remission) between participants in the two diet groups and estimated the prevalence of continuous, sustained remission for at least 2, at least 3, and at least 4 or 5 years. We examined the multivariate association of predetermined demographic (age and sex) and baseline risk factors (BMI, HbA<sub>1c</sub>, and fitness), and weight change with any remission. Physical and laboratory measurements from baseline through years of follow-up were modeled with generalized linear regression and generalized estimating equations. We used the Fisher exact test to analyze the percentage of patients achieving goals and compare categorical safety variables. All statistical tests were two-sided, and we present the results as means and SDs. A  $P$  value <0.05 was considered to indicate statistical significance. We conducted all analyses using SPSS, version 10.05 (SPSS, Chicago, IL).

### RESULTS

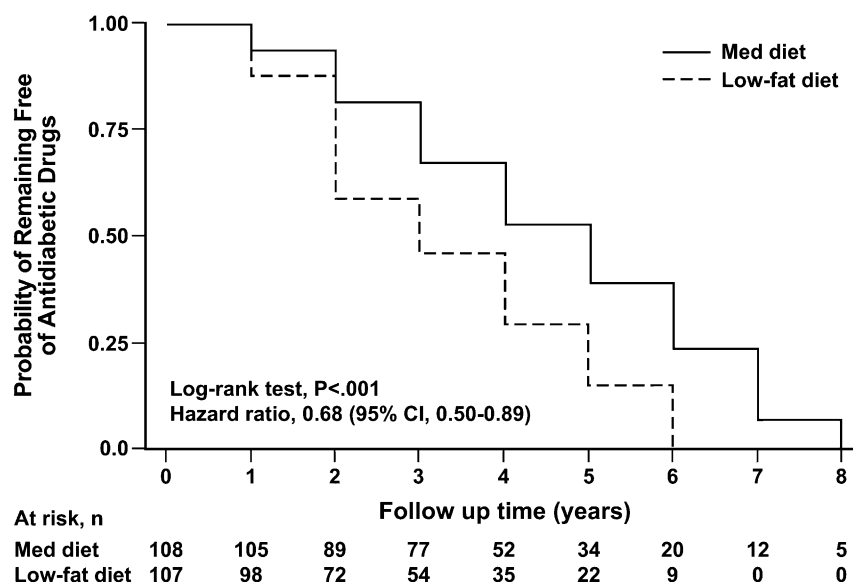
We randomly assigned 215 patients to either the LCMD or low-fat diet group (Supplementary Fig. 1). Equal numbers of patients withdrew from the groups during the trial. Baseline demographic and clinical characteristics were similar between treatment groups (Table 1). After the end of the core intervention (4 years), the cumulative incidence of participants with the primary end point (patients requiring pharmacological treatment for hyperglycemia) was 44% in the LCMD group and 70% in the low-fat group ( $P < 0.001$ ); the corresponding unadjusted hazard ratio (HR) was 0.63 (95% CI 0.51–0.86;  $P < 0.001$ ), and the HR adjusted for weight change was 0.70 (0.59–0.90). The analysis using HbA<sub>1c</sub> elevation >7% as the primary outcome gave comparable results (unadjusted HR 0.64 [95% CI 0.50–0.82];  $P < 0.001$ ).

All participants in the low-fat group reached the primary end point (need for diabetes medications) after a total follow-up of 6.1 years (median survival time: 2.8 years [95% CI 2.4–3.2]); all participants in the LCMD group reached the primary end point at 8.1 years of total follow-up (median survival time: 4.8 years [4.3–5.2]). The unadjusted HR for the overall follow-up was 0.68 (0.50–0.89;  $P < 0.001$ ) (Fig. 1) and that adjusted for weight change was 0.71 (0.55–0.88). The analysis using HbA<sub>1c</sub> elevation >7% (53 mmol/mol) as the primary outcome gave comparable results

**Table 1—Characteristics of the study participants**

Characteristic	Med diet (n = 108)	Low-fat diet (n = 107)
Sex (male/female), n	54/54	52/55
Age, years	52.4 (11.2)	51.9 (10.7)
Body weight, kg	86.0 (10.4)	85.7 (9.9)
BMI, kg/m <sup>2</sup>	29.7 (3.4)	29.5 (3.6)
HbA <sub>1c</sub> , %	7.75 (0.9)	7.71 (0.9)
HbA <sub>1c</sub> , mmol/mol	61.5 (5.6)	61 (5.6)
Glucose, mg/dL	162 (34)	159 (33)
Lipids, mg/dL		
Total cholesterol	221 (35)	216 (33)
HDL cholesterol	43 (10)	43 (10)
Triglycerides	171 (71)	168 (69)
Blood pressure, mmHg		
Systolic	139 (12)	140 (12)
Diastolic	87 (8)	86 (8)
Adiponectin, µg/mL	6.1 (2.1)	6.3 (2.3)
Smoking, %	21	22

Data are presented as mean (SD) unless otherwise indicated.



**Figure 1**—Probability of remaining free of antihyperglycemic drug therapy. Cumulative HR for the primary end point (need for diabetes medications).

(unadjusted HR 0.66 [0.52–0.90];  $P < 0.001$ ).

The prevalence of complete remission (glucose normalization) was more common in the LCMD group than in the low-fat diet group across all years of the study (prevalence ratio: 5.2 [95% CI 2.5–8.9];  $P < 0.001$ ). However, the absolute prevalence was low, ranging from 4.6% (2.4–3.2%) for LCMD versus 0.9% (0.4–1.4%) for low-fat diet ( $P < 0.001$ ) in year 1 to 2.4% (1.6–3.2%) for LCMD versus 1.3% (0.8–2.0%) for low-fat diet in year 2, to 2.5% (1.7–3.5%) for LCMD versus 0% for low-fat diet in year 3, and 1.9% (1.5–2.3%) for LCMD versus 0% for low-fat diet in year 4.

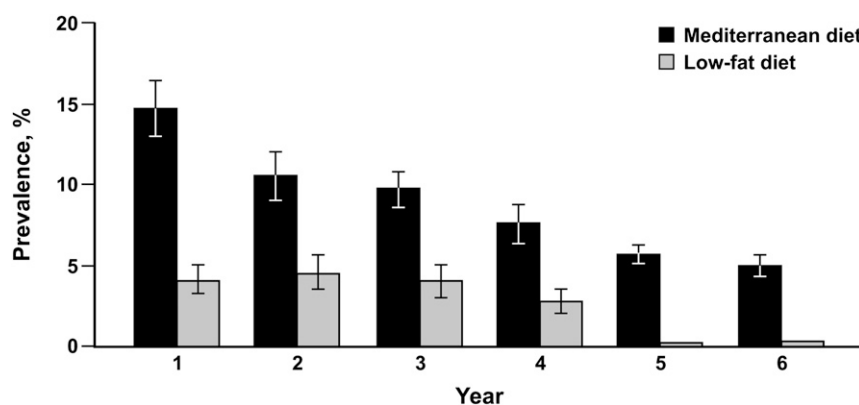
LCMD participants were significantly more likely to experience any remission (partial or complete), with a prevalence of 14.7% (95% CI 13.0–16.5%) during the first year, decreasing to 9.7% (8.6–10.7%) during year 3, and to 5.0% (4.4–5.6%) during year 6, compared with 4.1% (3.1–5.0%) at year 1, 4.0% (3.1–4.9%) at year 3, and 0% at year 6 in the low-fat diet group (Fig. 2). Accordingly, ratios of the prevalence of remission for LCMD versus low-fat diet ranged from 3.6 (2.5–5.1) in year 1 to 2.4 (1.4–3.5) in year 3 and 2.7 (1.5–4.2) in year 4.

The LCMD group was significantly more likely to have continuous, sustained

remission (Supplementary Fig. 2), as 9.7% (95% CI 8.6–10.7%) experienced at least a 3-year remission (vs. low-fat diet: 2.0% [1.4–2.6%];  $P < 0.001$ ) at some point during follow-up, 5.7% (4.9–6.9%) had at least a 4-year remission (vs. low-fat diet: 0%), and 2.9% (2.3–3.6%) had a 5-year remission (vs. low-fat diet: 0%). Except for lower baseline HbA<sub>1c</sub>, there were no significant interactions between any of the parameters considered and long-term remission.

#### Body Weight, Coronary Risk Factors, and ADA Goals

Participants in the LCMD group had significantly greater reduction in weight than



**Figure 2**—Prevalence of any remission by intervention and year. Data are prevalence and 95% CIs for any remission (partial or complete). Prevalence estimates were as follows: for Med diet, year 1: 14.7% (95% CI 13–16.5%) (15 of 102); year 2: 10.5% (9.0–12.5%) (9 of 85); year 3: 9.7% (8.6–10.7%) (7 of 72); year 4: 7.6% (6.5–8.6%) (4 of 52); year 5: 5.8% (5–6.6%) (2 of 34); and year 6: 5% (4.4–6%) (1 of 20); and for low-fat diet, year 1: 4.1% (3.1–5%) (4 of 97); year 2: 4.6% (3.5–5.6%) (3 of 64); year 3: 4% (3.1–4.9%) (2 of 50); year 4: 2.8% (2.1–3.4%) (1 of 35); year 5: (0 of 22); and year 6: (0 of 9).

did those in the low-fat diet group in the first year, with an absolute between-group difference in weight loss of 2.0 kg (Fig. 3), with no sex difference. The between-group differences were attenuated in the second year: at the sixth year, the mean difference in weight between the two groups was 0.4 kg (95% CI  $-0.1$  to  $0.7$  kg). However, the cumulative between-group differences were significant (main effect:  $-0.98$  kg [95% CI  $-1.5$  to  $-0.4$ ];  $P = 0.001$ ).

During the first year of follow-up, participants in the LCMD group had greater improvements than the low-fat group in HbA<sub>1c</sub> levels (main effect:  $-0.5$  [95% CI  $-0.6$  to  $-0.4$ ];  $P < 0.001$ ) (Fig. 3) and in all other measured cardiovascular risk factors (Supplementary Table 1). The between-group difference in cardiovascular risk factors diminished over time, with the HbA<sub>1c</sub> level and HDL cholesterol showing the most sustained differences. Equal proportions of patients used antihypertensive (24% LCMD and 23% low-fat diet) and lipid-lowering agents (15% LCMD and 16% low-fat diet) at the start of the trial. There were small and non-significant changes in these proportions during the trial (4-year data: 23% LCMD and 22.5% low-fat diet for antihypertensive agents; 13% LCMD and 16.5% low-fat diet for lipid-lowering agents).

The proportion of participants who met ADA goals for HbA<sub>1c</sub>, blood pressure, and LDL cholesterol increased in both groups, but the between-group difference in the increase was statistically significantly greater only for HbA<sub>1c</sub> in the Med diet group (Supplementary Table 2). The increase in proportion of

participants who met all three goals was statistically significantly greater in the Med diet group in the first 3 years of the trial.

#### Dietary Intake

The composition of the diets consumed by participants in the LCMD and low-fat diet groups did not statistically significantly differ at baseline. Daily energy intake decreased in both groups during the study without statistically significant between-group differences in any trial year (Supplementary Table 3). The percentage of carbohydrate intake decreased in the LCMD group compared with the low-fat diet group, and the percentage of monounsaturated and polyunsaturated fatty acid intake increased.

#### Physical Activity

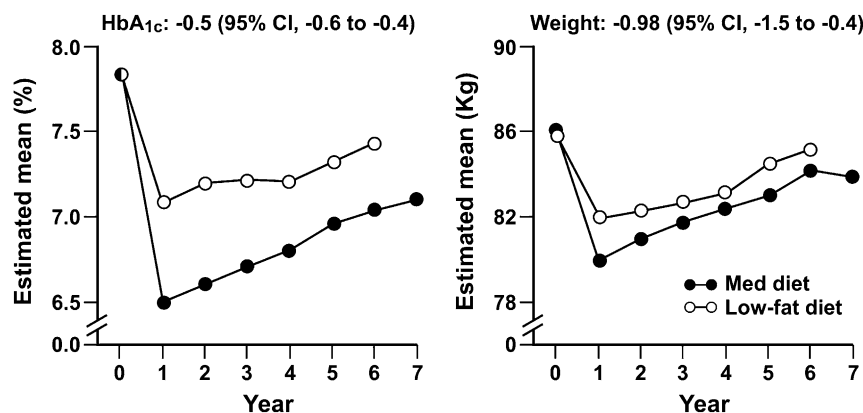
Participants in both groups increased the time they spent being physically active, with no statistically significant between-group difference in the amount of increase (Supplementary Table 3).

#### CONCLUSIONS

The postcore follow-up of the present trial, with a total follow-up of 8.1 years, makes it the longest study to assess the effects of a Med diet in patients with newly diagnosed type 2 diabetes. The results show that, compared with a traditional low-fat diet, an LCMD postpones the introduction of diabetes medications by  $\sim 2$  years; this effect was largely independent of weight loss. Moreover, partial or complete remission of diabetes, defined as a transition to prediabetic or normal glucose levels, respectively, occurred in 14.7%

of LCMD participants within the first year of intervention and 5% after 6 years; these rates were two to four times those of participants assigned to the low-fat diet group. In the Look AHEAD trial (14) involving 5,145 overweight or obese patients with type 2 diabetes, rates of any remission were notably higher (15–21%) among persons with substantial weight loss or fitness change, shorter duration of diabetes, or a lower HbA<sub>1c</sub> level at entry and those not using insulin. Owing to the different diabetes population included in our study (newly diagnosed), we were unable to assess the role of diabetes duration and insulin use; however, lower HbA<sub>1c</sub> at entry, but not weight loss, was a predictor of long-term remission.

Lifestyle intervention studies have shown the benefit of healthy lifestyle on delaying or postponing the deterioration of glucose tolerance to manifest type 2 diabetes (from 30 to 67%) (15,16). Moreover, a meta-analysis (3) of 10 studies yielded a 32% reduction of risk of future type 2 diabetes associated with healthy dietary patterns. Epidemiologic and interventional studies have revealed a protective effect of Med diets against chronic inflammation, insulin resistance, and the metabolic syndrome (6,17) associated with increased circulating levels of adiponectin (18,19). Moreover, one of the most desirable features of Med diets is the ability to improve coronary risk factors (17). Recently, the PREDIMED study (10), a randomized trial of the Med diet for the primary prevention of



**Figure 3**—Changes in HbA<sub>1c</sub> and weight during the years of follow-up. Shown are the changes from baseline in patients with newly diagnosed diabetes who received Med diet or low-fat diet. The reported main effect is the average of all between-group differences after baseline. Means were estimated with the use of generalized linear models for continuous measures.



cardiovascular events, was promptly terminated on the basis of an interim analysis that evidenced an impressive magnitude of benefit (~30% reduction of cardiovascular disease) in the two groups randomized to Med diets as compared with a control diet. As chronic inflammation is predictive of the future occurrence of both type 2 diabetes (20) and cardiovascular events (21), it is likely that the proposed anti-inflammatory effects of Med diets may play an important role in mediating their benefits on both glycemic status and cardiovascular risk.

The U.S. Dietary Guidelines recommend healthy dietary patterns, specifically the Dietary Approach to Stop Hypertension diet and Med diets (22). However, Med diets are not a single dietary pattern, although they share common features: these patterns are higher in fruits (particularly fresh), vegetables (emphasizing root and green varieties), whole grains (cereals, breads, rice, or pasta), and fatty fish (rich in omega-3 fatty acids); lower in red meat (and emphasizing lean meats); substituted lower-fat or fat-free dairy products for higher-fat dairy foods; and used oils (olive or canola), nuts (walnuts, almonds, or hazelnuts), or margarines blended with rapeseed or flaxseed oils in lieu of butter and other fats. These Mediterranean patterns are rich in total, monounsaturated, and polyunsaturated fat and are lower in saturated fat. Needless to say, low dietary intakes of fruits, vegetables, whole grains, or nuts and seeds or a high dietary intake of salt are individually responsible for 1.5% to >4% of the global disease burden (23). The total fat content of two Med diets tested in the PREDIMED study was 41% of energy intake; interestingly, a quite similar value (39%) was recorded in our study, as compared with 29.9% of energy intake in the low-fat diet, and the difference in fat content resulted mostly from increased monounsaturated fat intake.

While observational studies have shown that adherence to Med diets reduces the risk of death due to cardiovascular disease and cancer (24), there are very few long-term interventional studies with Med diets. In adjunct to reducing cardiovascular risk (10), the results of our study in newly diagnosed type 2 diabetic patients suggest that adopting an LCMD diet is associated with greater

likelihood to maintain longer glycemic control ( $HbA_{1c} < 7\%$  [53 mmol/mol]), greater likelihood of any remission of diabetes, and postponed (~2 years) need for diabetes medications. The ability to eliminate diabetes medications should considerably reduce medication costs, related adverse effects, risks of hypoglycemia, and hyperglycemic symptoms (25,26); even delaying the onset of diabetes can have a substantial effect on subsequent morbidity and therefore on the cost-effectiveness of diabetes prevention (27).

Some limitations of the current study have to be addressed. The unblinded nature of the study may have favored participants on the LCMD, as these participants could have been encouraged to try harder to get an  $HbA_{1c} < 7\%$  in the 3-month interval they were given to reinforce dietary guidance than participants on the low-fat diet. The analyses related to the postcore follow-up period of the trial were not planned in the original study protocol, and post hoc analyses have to be interpreted with caution. The postcore follow-up was not foreseen while calculating the original sample size, and because of low numbers of people at risk, the statistical power remains restricted. The low number of withdrawals is a marker of high commitment, and the generalizability of our findings in other populations must be studied. Remission of diabetes was not one of the intended primary objectives, making these analyses exploratory in nature. Moreover, the appropriate definition of diabetes remission remains an area of ambiguity and debate (28). In contrast, the study population was ideal for remission analysis because all diabetic patients included in the study were newly diagnosed and drug naive at an early stage of disease progression. Finally, the absence of another arm investigating the effects of a low-carbohydrate diet per se does not allow us to establish the hierarchy of benefits for the diabetic patients.

In spite of these limitations, this is the longest study, to our knowledge, to examine the effects of an LCMD in patients with newly diagnosed type 2 diabetes. Our findings suggest that a lower-carbohydrate Med diet resulted in a substantial long-term reduction of  $HbA_{1c}$  levels, higher rate of diabetes remission, and delayed need for diabetes

medication in patients with newly diagnosed type 2 diabetes.

**Funding.** This study was supported in part by the Second University of Naples and the Associazione Salute con Stile.

**Duality of Interest.** No potential conflicts of interest relevant to this article were reported.

**Author Contributions.** K.E. and D.G. researched data and wrote the manuscript. M.I.M. and M.P. contributed to discussion and reviewed and edited the manuscript. G.B. researched data, contributed to discussion, and reviewed and edited the manuscript. D.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

## References

- Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res Clin Pract* 2011;94:311–321
- Ezzati M, Riboli E. Behavioral and dietary risk factors for noncommunicable diseases. *N Engl J Med* 2013;369:954–964
- Esposito K, Kastorini CM, Panagiotakos DB, Giugliano D. Prevention of type 2 diabetes by dietary patterns: a systematic review of prospective studies and meta-analysis. *Metab Syndr Relat Disord* 2010;8:471–476
- Sacks FM, Bray GA, Carey VJ, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *N Engl J Med* 2009;360:859–873
- Mozaffarian D, Appel LJ, Van Horn L. Components of a cardioprotective diet: new insights. *Circulation* 2011;123:2870–2891
- Esposito K, Marfella R, Ciotola M, et al. Effect of a mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. *JAMA* 2004;292:1440–1446
- Shai I, Schwarzfuchs D, Henkin Y, et al.; Dietary Intervention Randomized Controlled Trial (DIRECT) Group. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N Engl J Med* 2008;359:229–241
- American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care* 2014;37(Suppl. 1):S14–S80
- Wing RR, Bolin P, Brancati FL, et al.; Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013;369:145–154
- Estruch R, Ros E, Salas-Salvadó J, et al.; PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013;368:1279–1290
- US Burden of Disease Collaborators. The state of US health, 1990–2010: burden of diseases, injuries, and risk factors. *JAMA* 2013;310:591–608
- Esposito K, Maiorino MI, Ciotola M, et al. Effects of a Mediterranean-style diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes: a randomized trial. *Ann Intern Med* 2009;151:306–314

13. IPAQ Research Committee. Guidelines for data processing and analysis of the International Physical Activity Questionnaire (IPAQ) [Internet], 2002. International Physical Activity Questionnaire. Available from <http://www.ipaq.ki.se/scoring.pdf>. Accessed 27 February 2014
14. Gregg EW, Chen H, Wagenknecht LE, et al.; Look AHEAD Research Group. Association of an intensive lifestyle intervention with remission of type 2 diabetes. *JAMA* 2012;308:2489–2496
15. Lindström J, Ilanne-Parikka P, Peltonen M, et al.; Finnish Diabetes Prevention Study Group. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *Lancet* 2006;368:1673–1679
16. Li G, Zhang P, Wang J, et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet* 2008;371:1783–1789
17. Esposito K, Giugliano D. Diet and inflammation: a link to metabolic and cardiovascular diseases. *Eur Heart J* 2006;27:15–20
18. Esposito K, Pontillo A, Di Palo C, et al. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. *JAMA* 2003;289:1799–1804
19. Esposito K, Giugliano D. Lifestyle and adiponectin level: four-year follow-up of controlled trials. *Arch Intern Med* 2010;170:1270–1271
20. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 2001;286:327–334
21. Duchatelle V, Kritikou EA, Tardif JC. Clinical value of drugs targeting inflammation for the management of coronary artery disease. *Can J Cardiol* 2012;28:678–686
22. Department of Agriculture, Center for Nutrition Policy and Promotion. Dietary guidelines for Americans [Internet], 2010. Available from <http://www.dietaryguidelines.gov>. Accessed 27 February 2014
23. Murray CJ, Lopez AD. Measuring the global burden of disease. *N Engl J Med* 2013;369:448–457
24. Sofi F, Abbate R, Gensini GF, Casini A. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. *Am J Clin Nutr* 2010;92:1189–1196
25. Bolen S, Feldman L, Vassy J, et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. *Ann Intern Med* 2007;147:386–399
26. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. *N Engl J Med* 2011;365:2002–2012
27. Herman WH, Hoerger TJ, Brandle M, et al.; Diabetes Prevention Program Research Group. The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. *Ann Intern Med* 2005;142:323–332
28. Buse JB, Caprio S, Cefalu WT, et al. How do we define cure of diabetes? *Diabetes Care* 2009;32:2133–2135