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Gardner CD, Landry MJ, Perelman D, et al. Effect of a ketogenic diet versus Mediterranean diet on glycated hemoglobin in individuals with prediabetes and type 2 diabetes mellitus: The interventional Keto-Med randomized crossover trial. *Am J Clin Nutr*. 2022;116(3):640-652.

What We Know, Think We Know, or Are Starting to Know

The place of low-carbohydrate diets in the management of type-2 diabetes [T2D] has been clouded by the excessive claims from low-carb proponents regarding the efficacy of these diets for T2D [(1)]. This is unfortunate for a more rational assessment of the evidence because the evidence does indicate a degree of utility for glycaemic control [(2,3)].

Low-carbohydrate diets lead to reductions in haemoglobin A1c, a marker of longer term [2-3 months] blood glucose regulation which are linear to the degree of carbohydrate restriction, i.e., greater carbohydrate restriction results in greater reductions in blood glucose levels [(2)]. However, these effects of low-carb diets appear to be short-term and observed primarily over 6 to 12-months; over 12 to 24-months, the effects of low-carb diets on HbA1c washout such that there are no significant difference between higher or lower carbohydrate diets on glycaemic control [(2,3)].

Low-carb aside, do you even do nutrition science without the Mediterranean diet? In a meta-analysis of studies comparing Mediterranean diets to control diets in individuals with T2D, the Med diets showed greater reductions in HbA1c and fasting blood glucose [(4)]. However, in a similar story to the low-carb diets, there is evidence that effects of a Med diet may also washout over 1-2 years [(5)].

One factor that emerges in this literature is a question over the optimal level of carbohydrates, and often the research diets labelled "low-carb" have an average of 30-35% energy [(2)], while low-carb advocates state that <26% of energy is a truer definition of low-carb [(1)]. Indeed, the most recent meta-analysis distinguished diets with between 26–45% carbohydrates and those with <26% energy or 130g total carbohydrate per day; low-carb diets with <26% energy did lead to greater reductions in HbA1c over 6-months [but not over 12-months] [(3)].

Christopher Gardner's research group at Stanford University have conducted several intervention trials comparing low-carb and low-fat diets, and a characteristic of the diets in their research is optimising basic nutrition best practices in both diets: emphasis on non-starchy vegetables and avoidance of refined grains, added sugars [(6)]. What happens when you optimise a ketogenic diet and overlap with a Mediterranean diet for T2D? The "Keto-Med study" tested this question.

The Study

The study was a randomised crossover trial comparing two diets:

- **"Well-Formulated Ketogenic Diet" [WFKD]**
- **"Mediterranean-Plus Diet" [MPD]**

To be included, participants were required to be classified as having prediabetes [HbA1c 5.7–6.4% or fasting blood glucose of 100–125 mg/dL] or T2D [HbA1c ⩾6.5% or fasting blood glucose ⩾126 mg/dL***;** for further detail, see ***Geek Box** below].

Both diets had three characteristics in common: maximise non-starchy vegetable intakes, and avoidance of refined grains and added sugars. The WFKD contained 20-50g/d carbohydrates, a 1.5g/kg bodyweight protein target, and remainder energy from fats. The diet emphasised unprocessed animal meats, cheeses, and oils [e.g., coconut oil or nut oils]; legumes, wholegrains, and fruits were avoided.

The MDP followed the "Mediterranean Diet Pyramid" and was a primarily plant-based diet, with fish as the main protein source and olive oil the primary fat source. The diet emphasised legumes, wholegrains, and fruits, while meats, poultry and dairy were minimised.

As a crossover design, participants were randomised to the order of diet, i.e., MDP>WFKD or WFKD>MDP. Diets were followed for 12-weeks before participants crossed over immediately to the alternate diet [no washout period in between diets]. There was a 12-week follow-up period after the end of the 24-week intervention. All meals were prepared and delivered to participants for the first 4-weeks of each diet, after which the participants prepared their own food. Energy restriction and weight loss were not prescribed.

The primary outcome was change in HbA1c over 12-weeks between the diets. Secondary outcomes included changes in fasting glucose and insulin, blood lipids, and weight.

*Geek Box: Diabetes Definitions

There are several markers used in the assessment of blood glucose regulation. The following table sets out the various blood glucose ranges used in the UK, note that these ranges may differ slightly in other countries. The table has the ranges for each stage of glucose tolerance [left hand column], for both fasting glucose levels [middle column] and the 2hr postprandial glucose response to an oral glucose tolerance test [right hand column].

Glucose Tolerance State	Fasting Plasma Glucose	2hr Plasma Glucose (OGTT)
Normoglycaemic	4.0–5.4mmol/L [72–99mg/dL]	Up to 7.8mmol/L (140mg/dL)
Impaired Fasting Glucose [IFG]	5.5–6.9mmol/L [100-125mg/dL]	7.8–11.0mmol/L [140–199mg/dL]
Impaired Glucose Tolerance [IGT]	<7.0mmol/L [<126mg/dL]	7.8–11.0mmol/L [140–199mg/dL]
Combined IFG/IGT	5.5–6.9mmol/L [100-125mg/dL]	7.8–11.0mmol/L [140–199mg/dL]
Type 2 Diabetes [T2D]	>7.0 mmol/L [>126mg/dL]	>11.1 mmol/L [200mg/dL]

The levels for IFG and IGT are considered 'pre-diabetes'. There is also glycated haemoglobin A1c [HbA1c], a marker for when red blood cells are exposed to glucose levels in plasma. HbA1c reflects longer-term blood glucose regulation over the period of the previous 3-months and is expressed as a percentage. Currently, 6.5% is considered the threshold for a diagnosis of T2D, and the range of 6.0–6.4% is considered 'high-risk' according to World Health Organization guidelines.

It is helpful to have an idea of the various levels of glucose tolerance, given the continuum of glucose tolerance. Although attention tends to be put on the diagnosis of a disease itself, in this case T2D, in reality the underlying pathophysiology precedes diagnosis by years. This explains the need for early intervention in the natural history of the disease.

Results: 33 participants completed the trial, with an average age of 60yrs. 61% of participants had prediabetes and 39% had T2D. 61% were male, 45% were non-Hispanic White ethnicity, and 85% were university graduates in educational attainment.

Dietary adherence [more under ***Interesting Finding***, below] was higher for both diets during the food delivery phase compared to the self-preparation phase of each diet. Energy intake during both diet phases was an average of 250–300kcal lower compared to baseline.

- ***Primary Outcome – HbA1c*:** There was no significant difference between diets; both diets improved glycaemic control with the WFKD lowering HbA1c by 9% [95% CI 7% to 11%] and the MDP by 7% [95% CI 5% to 9%].
- ***Secondary Outcomes*:** Bodyweight decreased significantly in both groups, with an effect of diet order noted; participants randomised to begin with the WFKD lost more weight in that diet phase compared to those who began with the MDP. At the end of the first diet phase, participants who began with the WFKD lost an average of 7.5kg compared to 5.1kg on the MPD. The WFKD led to significant increases in LDL-C, HDL-C, and decrease in triglycerides.

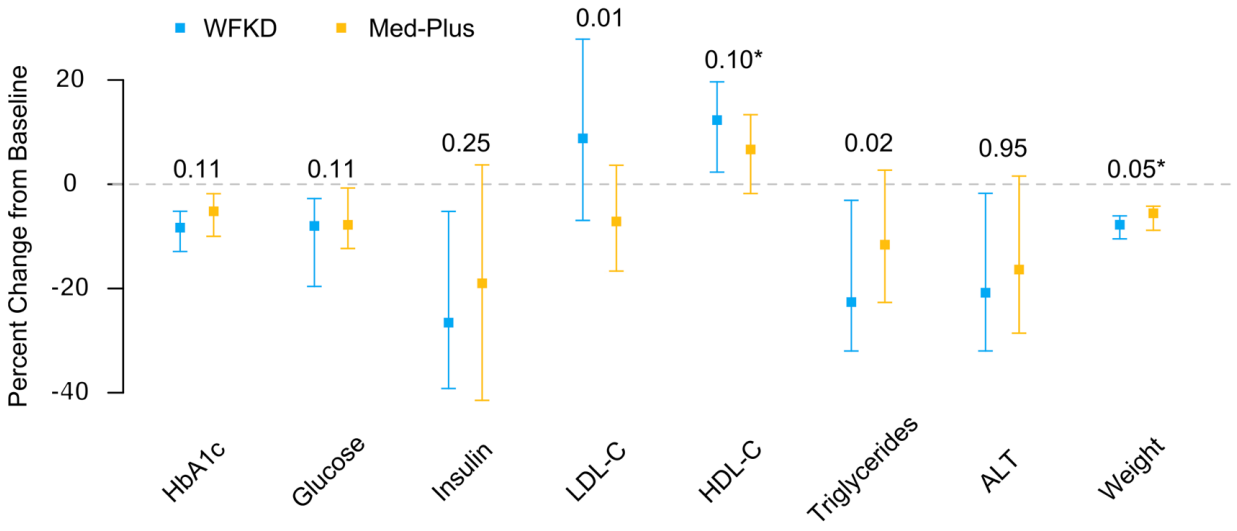


***Figure** from the paper illustrating the change in the primary outcome [**HbA1c; far left**] and secondary outcomes in the WFKD [**blue boxes**] and MPD [**yellow boxes**]. Changes are presented as percentage from baseline in each diet group.*

- ***Sensitivity Analysis – Effects of Weight Loss on HbA1c*:** There was no significant differences observed between diets when baseline bodyweight and weight loss were analysed in relation to changes in HbA1c. In effect, weight loss explained the improvement in HbA1c, not the type of diet.

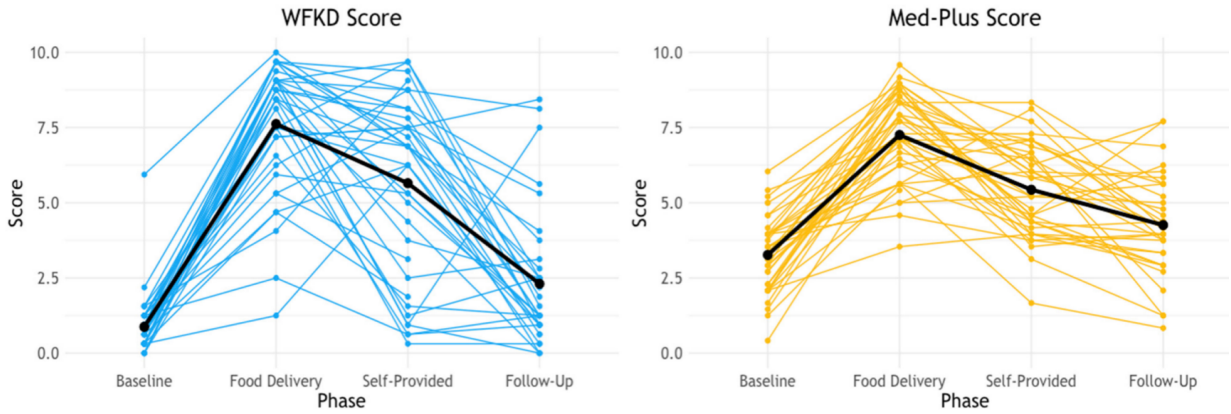
The Critical Breakdown

Pros: The trial was pre-registered at ClinicalTrials.gov and there are no apparent deviations from the pre-registered protocol. Randomisation method was appropriate [computer-generated by a statistician not involved in the study], and stratified according to prediabetes or T2D status in order to ensure that both groups were balanced for glycaemic status. The crossover design allowed for each participant to act as their own control, minimising inter-individual variation between diets influencing the outcomes. At time points throughout the study [weeks 0, 4, 12, 16, 24, and 36], diet was assessed by 3 unannounced 24-hour recalls [2 weekdays, 1 weekend] administered by a trained nutritionist, and the average of all 24-hour recalls used to determine adherence to the diets. The statistical analysis was thorough and included a sensitivity analysis to determine the influence of weight loss on HbA1c.

Cons: The curse of nutrition interventions, this was ultimately a very small sample size which limits the wider generalisability of the findings. There was no washout period between diets, and although no interaction effects were noted for most findings, the order of diet did influence certain outcomes, e.g., weight loss and HbA1c improvements slightly greater when participants started with the WFKD. The trial was disrupted by COVID-19, which affected the timing of blood sampling from participants, the duration certain participants remained on their diets, and the delivery of food to some participants. The investigators did the best they could in the circumstances, and still managed to gather a usable data set [i.e., the primary analysis was confined only to complete data], however, it may have influenced some outcomes if total duration of dietary adherence differed.

Key Characteristic

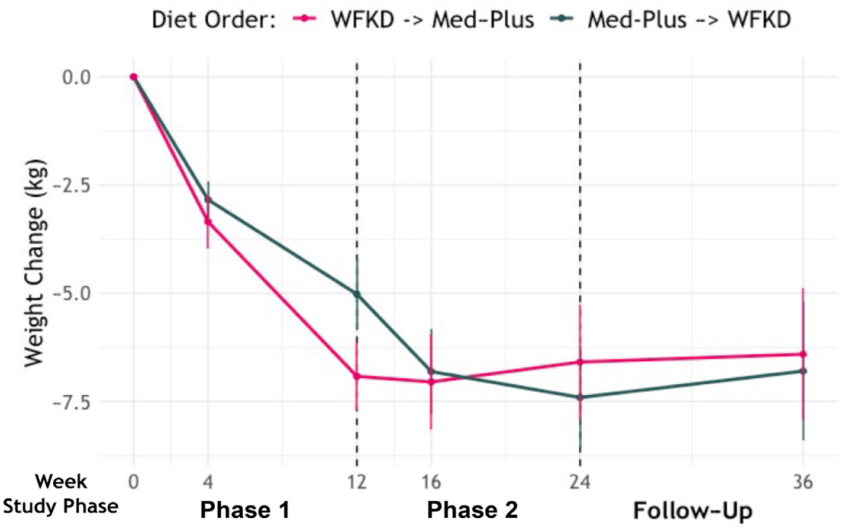
Analysis of this trial has been illuminating for perhaps the most deterministic factor influencing outcomes on any diet, irrespective of macronutrient content and food selections: adherence. This research group previously published data on adherence from the Keto-Med trial, which as you can see from the **figure** below indicated that adherence was highest for both diets when food was delivered to participants, and declined steadily over the self-provision period and into the follow-up period.



During the food delivery phase, adherence [1-10 scale, with 10 highest] was 7.6 and 7.3 on the WFKD and MDP, respectively. During the self-provision phase, adherence scores were also similar at 5.7 and 5.4 for the WFKD and MDP, respectively. However, during the follow-up period this dropped to 2.3 and 4.3 for the WFKD and MDP, respectively, indicating that when once back to their relatively habitual diets the dietary pattern more resembled the MDP than the WFKD. And this is crucial, because ultimately, independent of macronutrient content, adherence is the best predictor of outcomes with dietary interventions [7,8].

Interesting Finding

The lack of effect of diet type, rather than weight loss, is interesting insofar as it adds to a body the evidence indicating no particularly unique effect of diet independent of weight loss. It also adds to the body of evidence that shows that low-carb diets may provide a "head start" in the short-term, but typically the advantage in weight loss and glycaemic control washout in the long-term [2,3].



In the study, participants lost more weight when starting with the WFKD; when starting with the MPD, participants lost more weight after transitioning to the WKFD. Overall, these differences were small and did not correspond to meaningful differences in HbA1c. This latter point is important; the magnitude of change in HbA1c was greater when starting with the WFKD; a decrease of 0.64% vs. 0.32% compared to the MPD. But this largely washed out by the end of both phases, such that the average reduction in HbA1c was similar between diets.

All in all, the data tells us nothing beyond what we already knew; that improvements in HbA1c will be proportional to the magnitude of weight loss, and the type of diet is secondary [7,9,10]. Importantly, the level of carbohydrate restriction may only be relevant in the short-term, and benefits to glycaemic control tend to fall away over 6 to 12-months [2,3,7,9].

Relevance

Christopher Gardner's research group have produced some excellent nutrition intervention trials, most notably the DIETFITS study, which found no significant differences between healthy dietary patterns either low in fat or carbohydrate on weight loss or metabolic outcomes [6]. And while the thoughtful design and ambition of the present intervention is commendable, ultimately the Keto-Med trial provides little additional insights into the role of diet in the management of T2D.

The primary addition of this study is the matching of some key characteristics between diets; emphasising non-starchy vegetables, minimising added sugars and refined grains. Nevertheless, the WFKD still omitted food groups like legumes and wholegrains, and led to significant increases in LDL-C. Thus, for the modest improvements in HbA1c it may not be worth the trade-off of increased cardiovascular risk factors. That is not necessarily validation by default of the Med diet, which yielded similar outcomes overall but with the bonus of a modest reduction in LDL-C.

Let's consider the absolute changes in HbA1c from both diets, which decreased from 6.28% to 5.72% on the WFKD>MDP diet order and 6.12% to 5.71% on the MDP>WFKD diet order. In effect, participants started out in a high-risk HbA1c range and ended up at the lower end of the risk range. This is unlikely to have any meaningful impact on progressive deterioration of disease severity over the longer term [11,12].

Application to Practice

At this point, it is difficult to argue in favour of any particularly unique effect of low-carb diets for T2D management, beyond the potential for more immediate weight loss and related glycaemic control over 3 to 6-months, benefits that would we not expect to see after 1-year [2,3,7,9]. For the Mediterranean diet, we could say the same thing; modest improvements in HbA1c in the short-term [4].

Ultimately, this evidence comes back to the reality that the primary driver of prevention of progression from impaired glucose tolerance or 'prediabetes' to T2D was weight loss, achieved through achievement of dietary and physical activity targets [13]. The challenge for meaningful reductions in T2D risk and management are the degree of weight loss required and the need to maintain that weight loss in the context of continued declining beta-cell function.

From the perspective of T2D management, at least the Keto-Med trial provides further evidence that the composition of the diet is a secondary consideration to weight loss.

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