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Economic Evaluation

Economic Evaluation of Fasting Mimicking Diet vs Standard Care in Diabetic Patients on Dual or Triple Medications at Baseline in the United States: A Cost-Utility Analysis

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ABSTRACT

Objectives: According to most guidelines, dietary interventions are essential in the management of diabetes. Fasting has emerged as potential therapeutic regimes for diabetes. The proof-of-concept study and the fasting in diabetes treatment trial are the first to explore the clinical impact of the Fasting Mimicking Diet (FMD) in patients with type 2 diabetes mellitus. Their results showed that FMD cycles improve glycemic management and can be integrated into usual care complementary to current guidelines. This economic evaluation aims to assess the 10-year quality-of-life effects, cost implications, and cost-effectiveness of adding a 3-year FMD program to diabetes standard care in diabetic population on dual or triple medications at baseline from the perspective of the US payer.

Methods: We constructed a microsimulation model in TreeAge using a published US-specific diabetes model. The model was populated using FMD effectiveness outcomes and publicly available clinical and economic data associated with diabetes complications, use of diabetes medications, hypoglycemia incidence, direct medical costs in 2021 USD, quality of life, and mortality. All benefits were discounted by 3%.

Results: This cost-utility analysis showed that the FMD program was associated with 11.4% less diabetes complications, 67.2% less overall diabetes medication use, and 45.0% less hypoglycemia events over the 10-year simulation period. The program generated an additional effectiveness benefit of 0.211 quality-adjusted life year and net monetary benefit of 41 613 USD per simulated patient. Thus, the FMD program is cost saving.

Conclusions: These results indicate that the FMD program is a beneficial first-line strategy in T2DM management.

Keywords: cost-utility analysis, economic evaluation, Fasting Mimicking Diet, nutritional therapy, type 2 diabetes.

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Highlights

- Diabetes is an epidemic in the United States, with over 34 million Americans suffering from the condition. Dietary interventions can safely and effectively reduce weight and improve glycemic control in diabetic patients. According to most guidelines, they are considered essential in the management of the disease. The periodic 5-day Fasting Mimicking Diet (FMD) can improve glycemic management in patients with type 2 diabetes and can be integrated into usual care complementary to current guidelines.
- By targeting the root cause of type 2 diabetes, results from FMD clinical trials suggested a viable, nutrition-led intervention that enhances the effectiveness of the standard of care. This cost-utility study is the first to evaluate the costs and consequences of adding the FMD fasting nutri-technology to diabetes standard care from the perspective of the US healthcare payer.
- The FMD program is associated with significantly lower diabetes-related events in diabetic population on dual or triple medications at baseline, resulting in an additional effectiveness benefit of 0.211 quality-adjusted life year and net monetary benefit of 41 613 USD per simulated patient over 10 years. Because this program is cost saving, our results indicate that the FMD is a beneficial first-line strategy in type 2 diabetes mellitus management, allowing the possibility of diabetes regression to be within reach.

Introduction

Diabetes is a disease of aging, characterized by insulin resistance and diminished insulin secretion.[1] It imposes a substantial burden on society in the form of higher medical costs, lost productivity, premature mortality, and reduced quality of life (QOL).[2] Type 2 diabetes mellitus (T2DM) develops as a result of genetic, environmental, and behavioral factors, including sedentary lifestyle and energy-rich, nutrient-poor diet, both of which predispose to obesity.[3] In the United States, 34.1 million adults had diabetes, notably T2DM, and the disease is the seventh most common cause of death.[4] The total economic burden of diabetes in the United States was estimated at 404 billion US dollar (USD) in 2017, amounting to a hidden tax of 1240 USD per American.[5]

Glycemic control with glucose-lowering medications in patients with T2DM is an established standard of care.[6] However, maintenance of glycemic targets with monotherapy is often possible for only a few years, after which more intensive combination therapy is necessary.[7] Poor medication adherence is a common phenomenon among patients with diabetes,[8] notably in those prescribed complex polypharmacy regimen due to lack of affordability[9]

and fear of potential adverse effects, particularly hypoglycemia.[10] Thus, medication-based diabetes' standard care aims to mostly slow disease progression rather than reversing it.

Diabetes is traditionally thought to be a chronic, progressive, incurable condition, even though T2DM is highly correlated to lifestyle and biological aging and can benefit from changes in diet and nutrition. Modest and sustained weight loss have been shown to improve glycemic control and to reduce the need for glucose-lowering medications.[11,12] Small studies have demonstrated that very-low-calorie diets (defined as less than 800 Kcal per day) can reduce glycated hemoglobin (HbA1c) level to less than 6.5% in the absence of pharmacologic therapy or ongoing procedures.[13]

The Fasting Mimicking Diet (FMD; Supplemental Material found at https://doi.org/10.1016/j.jval.2024.08.003) is a 5-day low-calorie, low-protein, and low-sugar diet but with relatively high amounts of plant-based complex carbohydrates and healthy fats that mimics the effects of water-only fasting on markers associated with stress resistance or longevity. It is an emerging nutri-technology focused on applying food as medicine to accompany or replace pharmacological therapies.[14] FMD is a promising intervention in the realm of integrative and lifestyle medicine to improve overall health.[15] Studies have so far demonstrated that periodic FMD cycles are associated with a range of beneficial effects, including the promotion of stem cell regeneration,[16-18] improving anticancer immunity, and lessening of chemotherapy side-effects in patients with cancer,[19-21] improved cardiometabolic risk factors in overweight or obese people,[22] improved cognitive performance in early Alzheimer's disease,[23] and lowering risk factors for cancer, diabetes, and heart disease.[24]

FMD affects the root cause of T2DM through targeting factors such as cellular rejuvenation, muscle protection, weight loss, insulin sensitivity, and potentially reduced biological age score.[25] The proof-of-concept study is, to our knowledge, the first randomized controlled design study to explore the clinical impact of the FMD in patients with T2DM. The study showed that when accompanied by intensive diabetes care, FMD cycles are safe, well tolerated, and can be integrated into standard care. The study demonstrated that FMD improves major critical diabetes metrics within 6 months, including body weight, body mass index (BMI), HbA1c levels, and disease remission.[26] In the fasting in diabetes treatment (FIT) trial, which has only included patients with T2DM who are treated with lifestyle advice only or with metformin, the use of the FMD program in a real-world setting improved glycemic management in a substantial proportion of patients.[27] These results suggest a viable, nutrition-led intervention that enhances the effectiveness of the standard care, allowing the possibility of diabetes regression to be within reach.

As nutrition-based healthcare interventions are increasingly taking an important part in the management of diabetes, to our knowledge, this cost-utility study is the first to evaluate the 10-year costs and consequences of adding the FMD program to diabetes standard care in diabetic population on dual or triple medications at baseline from the perspective of the US payer and using a published US-specific diabetes model, the US T2DM Policy Model (UST2DPM).[28]

Methods

Model Overview

A brief overview of the UST2DPM is provided here, with additional details found in the Supplemental Material found at https://doi.org/10.1016/j.jval.2024.08.003and elsewhere.[28] The UST2DPM is an individual patient-level, Monte Carlo-based Markov model of the incidence, prevalence, mortality, and costs related to T2DM among US adults.[28] The model, depicted in Appendix Figure 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.08.003, integrates diabetes-related complications and mortality modules from the United Kingdom Prospective Diabetes Study-Outcomes Model 2 (UKPDS-OM2)[29] with a hypoglycemic event module and an American Diabetes Association (ADA)/European Association for the Study of Diabetes-based diabetes medication algorithm. The model comprised 5 health states (diabetes without macrovascular and microvascular complications, diabetes with a history of macrovascular complications, diabetes with a history of microvascular complications, diabetes with a history of both macrovascular and microvascular complications, and death). Simulated patients may start in any of the 4 nondeath diabetes health states.[28,30] During each cycle, a patient may develop diabetes-related macrovascular complications (coronary heart failure, ischemic heart disease, myocardial infarction, and stroke) and microvascular complications (amputation, blindness, foot ulcer, and renal failure). Likelihood of complications was based on simulated patients' baseline demographic and clinical characteristics, evolving risk factors, and history of diabetes-related complications. An event is deemed to have occurred by comparing estimated probabilities with random numbers derived from a 0-to-1 uniform distribution. Simulated patients may experience only 1 macrovascular or microvascular complication per year. The occurrence of a second myocardial infarction, stroke, or amputation event is described in the model. Diabetes-related complications are associated with increased mortality rates in the year of the event occurrence and in the subsequent years according to the mortality equations developed in the UKPDS-OM2.[29] Based on epidemiological data, there is no excess risk of death from diabetes without complications.[31]

In this cost-utility analysis, the number of diabetes medications at baseline was derived from an analysis of the use of antihyperglycemic medications in US adults[32] restricted to patients with HbA1c over 7.0% and with probabilities rearranged to include only dual and triple medications. The choice of diabetes medications at baseline was updated based on the proportion of its use in the United States as a second- or third-line agent from reported literature.[33] Simulated patients may also have an addition or a removal of a medication based on achieving their HbA1c target, which was assumed at 7.0% as considered in the UST2DPM for the uniform intensive glycemic control group.[28] The model assumed that a patient' medications would increase (decrease) in the year after their HbA1c value increased above (decreased below) 1% of the predetermined threshold. Each added medication, according to published probabilities,[33] would reduce the HbA1c level by 1.0%.[28,34] In case of removal, the last line medication was stopped. The risk for hypoglycemia is simulated based on use of diabetes medications[35] and assuming that severe hypoglycemia was associated with a greater decrease in utility than mild or moderate events and that only severe hypoglycemic events increased the probability of healthcare use.[36,37]

Event rates, costs and utilities were derived from the UST2DPM, UKPDS-OM2, and a variety of peer-reviewed publications and publicly available sources (Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.08.003). The outcome of this analysis was the incremental cost per quality-adjusted life-year (QALY) gained.

Simulated Patient Cohorts

Simulated patient cohorts were defined with baseline demographics, baseline diabetes-related complications, and baseline use of diabetic medications (dual or triple therapy). Baseline

characteristics of a simulated patient were primarily sampled from distributions derived from the National Health and Nutrition Examination Survey 2011 to 2012 as reported in the UST2DPM,[28] with supplemental data to complete the patient profiles (Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.08.003). At baseline, the mean age of the simulated cohorts was 63.1 years (standard deviation [SD] 11.6 years), with a mean duration of diabetes of 10.4 years (SD 9.1 years), mean BMI of 31.9 kg/m^2 (SD 7.4 kg/m^2), 46.6% female, and 39.5% with macrovascular and/or microvascular complications. HbA1c at baseline was derived from the FMD proof-of-concept study (8.1% [SD 0.4%])[26] because it better reflects the targeted population (ie, diabetic patients on dual or triple medications therapy) than that in National Health and Nutrition Examination Survey (ie, the general diabetic population in the United States).

FMD Program Effectiveness

In the proof-of-concept study, FMD led to significant reductions in body weight (−9.9 kg), BMI (−3.3 kg/m^2), and HbA1c (−1.4%) after 6 months.[26] The reduction in BMI and HbA1c corresponded to a relative risk reduction of 10.6% and 17.3%, respectively, compared with baseline. After 6 FMD cycles, antihyperglycemic medications were reduced in 67% of participants in the FMD group compared with baseline. In the FIT trial, FMD led to significant reductions in body weight (−3.7 kg), BMI (−1.3 kg/m^2), and HbA1c (6.0 mmol/mol in fully compliant FMD participants and excluding outliers) after 12 months.[27] The reduction in BMI and HbA1c corresponded to a relative risk reduction of 4.3% and 7.6%, respectively, compared with baseline. Medication use decreased in 47% of participants in the FMD group compared with 5% of controls.

The proposed duration of the FMD program in patients with diabetes is 3 years. FMD compliance rate was reported at 69.8% in the FIT trial and 81.0% in the proof-of-concept study. In a noncompliance case, we assume that the FMD program would be stopped within the first year. The drop-out rate was assumed at 8.4% after the first year and at 13% after the second year of the program, as reported on average for diabetes medications.[33]

A cost-utility analysis adopts an optimistic assumption that the effect of an intervention will persist for life and/or a pessimistic assumption that the effect of that intervention will persist only for the intervention period.[38] In the FMD program, simulated patients are assumed to retain 54.5% of the treatment effect in after year 1 and 43.2% in after year 2 for BMI, as reported for national lifestyle intervention programs in real-world settings.[39] The same is empirically assumed for HbA1c.

Results from both trials are combined to model FMD program effectiveness based on the baseline HbA1c level (Supplemental Material found at https://doi.org/10.1016/j.jval.2024.08.003). Patients in the proof-of-concept study have more advanced diabetes than those in the FIT trial as shown by their baseline HbA1c level (8.1% vs. 6.9%, respectively). Given that HbA1c at baseline is assumed to vary between 7.3% and 8.9% (representing +/− 2 SD) for this simulated population group, the relative rates are de facto those estimated in the proof-of-concept study.

Health-Related QOL Calculation

QALY, the preferred method for measuring health outcomes, combines the length of life and the preference weight for a particular health state into a single measure.[40] Using established utility values in patients with T2DM in the United States, the independent QOL effects of diabetes-related complications,[41] hypoglycemia events,[42] and use of diabetes medications[28] were captured in the model by applying event disutility in the year and, if appropriate, in each subsequent year after a complication has occurred (Appendix Table 1 and Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.08.003). Additionally, disutility associated with aging[43] and with an excess BMI (above 25 kg/m^2)[41] was also considered. It is assumed that multiple complications have an additive effect on utility.[41,44] To prevent very low or negative health utility scores, health utility was censored to 0.300, which represents the minimum score for a living person.[45]

Valuation of Costs and Perspective

Costs associated with diabetes-related complications, severe hypoglycemia, medication use, and self-monitoring were included in the model (Appendix Table 1 and Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.08.003). Noninsulin oral diabetes medication costs were calculated using the average wholesale price across drug classes.[46] Drug acquisition cost for insulin was obtained from the 2018 Red Book.[47] Direct costs were accounted from the US healthcare payer's perspective, and were inflated to 2021 USD using the medical component of the US consumer price index (https://beta.bls.gov/dataViewer/view/timeseries/CUUR0000SAM).

FMD Program Cost

The monthly cost of the FMD program is 399 USD for the first year and 250 USD for the second and third years.

Comparator

In this cost-utility analysis, the FMD program is proposed as a supplement to standard care and is compared with standard care alone option to calculate the incremental cost-effectiveness ratio (ICER). The ADA endorses a patient-centered approach to diabetes standard care consisting of metformin as first-line therapy, with sequential addition of other drug therapies to meet glycemic targets[48,49] (Supplemental Material in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.08.003).

Time Horizon and Discounting

Because the longer the time horizon the lower the probability that assumptions made today will still hold in the future,[50] we have assumed a 10-year time horizon. A 1-year cycle length was considered because it is the most commonly used in the modeling of diabetes dynamics,[28] and to handle the complexity of the microsimulation model (Supplemental Material in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.08.003).

According to the guidelines produced by the US Public Health Service Panel on Cost-Effectiveness in Health and Medicine, future costs and benefits were discounted at a rate of 3.0% per year.[51]

Statistical Approach

A microsimulation model was constructed using TreeAge Pro Healthcare version 2022 R2.1 (TreeAge Software Inc) to assess long-term benefits, costs and cost-effectiveness of FMD program in patients with T2DM (Appendix Fig. 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.08.003). Simulated cohorts of 25 000 patients with the same individual baseline characteristics derived from the distributions shown in Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.08.003 were assigned to both strategy options. For each cycle, the model accrued a cost and QALY, which were summed at the end of the simulation resulting in estimates of the expected costs and the average number of QALYs for each participant. Trackers were used to record information on

individual patient events (Supplemental Material found at https://doi.org/10.1016/j.jval.2024.08.003).

Sensitivity Analysis

Parameter uncertainty can be assessed through a deterministic sensitivity analysis (DSA) or a probabilistic sensitivity analysis (PSA). In the DSA, the sensitivity ranges of model's parameters varied individually according to their 95% confidence interval or plausible ranges reported in the literature, or otherwise within 30% of the mean estimates (Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.08.003). In the PSA, the parameters varied collectively over their listed ranges, with 1000 recalculations of the ICER ratios based on random draws from the parameter distributions (Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.08.003). Additional population scenarios (ie, general diabetic population in the United States and newly diagnosed patients with T2DM) were considered and are shown in the Supplemental Material in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.08.003.

Results

Base-Case Analysis

Based on FMD trial data, simulated patients in the FMD group are expected to have better outcomes than those in the standard care alone group (Table 1). The FMD program was associated with 11.4% less diabetes complications (including 7.9% and 9.7% less first- and second-event macrovascular complications, respectively, and 25.5% and 16.6% less first- and second-event microvascular complications, respectively), 67.2% less overall diabetes medication use (including 72.0% less insulin use), and 45.0% less hypoglycemia events (including 51.7% and 40.3% less severe hypoglycemic events requiring emergency department visits and hospitalization, respectively) over the 10-year simulation period. The number needed to treat to avoid one diabetes-related complication (any), one diabetes medication use (any), and one hypoglycemic event (any severity) is estimated at 17.8, 0.6 and 0.5 patients, respectively.

Simulated patients in the FMD group are expected to have an additional 0.211 QALY per patient over the 10-year simulation period (or approximately 77 quality-adjusted days). Nearly 43% of this QALY gain is due to lower overall diabetes medication use and 17% due to lower excess BMI in the simulated FMD group compared with the simulated standard care alone group (Table 2). Simulated patients in the FMD group are expected to have 49 204 USD lower direct medical costs per patient over the 10-year simulation period. This monetary benefit is mainly driven by lower overall diabetes medication use, accounting for 94.7% of the total monetary benefit and representing 60.6% lower medication cost compared with simulated patients in the control group. The weighted cost of the FMD program in this population group is estimated at 7590 USD over the 3 years duration of the program. Overall, the incremental cost of using the FMD program in diabetic population on dual and triple medications at baseline resulted in net monetary benefit of 41 613 USD per simulated patient (Table 3).

Because the FMD program would cost less than the standard care alone, the plan is cost saving or dominant per ICER terminology. From a budget impact perspective, the program is expected to generate income (ie, monetary benefit exceeding plan cost) and to break-even (ie, cumulative monetary benefit exceeding cumulative cost) within the first year.

Table 1. General outcomes for the diabetic population on dual and triple medications at baseline.

Outcomes	Standard care	FMD	Difference in strategies	
			Absolute	Relative (%)
Macrovascular complications (1st events)	0.3462	0.3187	−0.0274	−7.9
Microvascular complications (1st events)	0.0828	0.0617	−0.0211	−25.5
Total complications (1st events)	0.4290	0.3804	−0.0486	−11.3
Macrovascular complications (2nd events)	0.0468	0.0422	−0.0046	−9.7
Microvascular complications (2nd events)	0.0176	0.0146	−0.0029	−16.6
Total complications (2nd events)	0.0644	0.0569	−0.0075	−11.6
Total complications (1st and 2nd events)	0.4933	0.4373	−0.0560	−11.4
1st line diabetes medication use	1.000	0.441	−0.559	−55.9
2nd line diabetes medication use	0.968	0.299	−0.670	−69.1
3rd line diabetes medication use	0.629	0.113	−0.515	−82.0
Mean medication use per year	2.60	0.85	−1.74	−67.2
Insulin use (1st, 2nd, and 3rd lines)	0.469	0.131	−0.338	−72.0
Mild-to-moderate hypoglycemic events	3.71	2.10	−1.61	−43.3
Severe hypoglycemic events	0.99	0.49	−0.51	−51.0
Total hypoglycemic events	4.71	2.59	−2.12	−45.0
Severe events requiring ED visits (%)	2.6	1.3	−1.4	−51.7
Severe events requiring hospitalization (%)	0.7	0.4	−0.3	−40.3

ED indicates emergency department; FMD, Fasting Mimicking Diet.

Sensitivity Analysis

The DSA (Appendix Table 3) demonstrated that FMD-generated monetary benefit was most sensitive (explaining more than 10% variability in either direction; Fig. 1) to variation in the time horizon, patient' characteristics at baseline, assumptions on the benefits of FMD program seen in trials, cost of diabetes medications, HbA1c threshold for glycemic control, and annual discount rate. To note, the sensitivity to the HbA1c level at baseline was dependent on the HbA1c threshold for glycemic control. For example, increasing the HbA1c threshold to 8.0% diminishes the effect of high HbA1c at baseline. This meant that patients with extreme HbA1c at baseline targeting a strict HbA1c goal would

Table 2. QALY calculation for the diabetic population on dual and triple medications at baseline.

Variable	Standard care	FMD	Difference in strategies	
			Absolute	Relative (%)
Life years (not discounted)	8.616	8.705	0.089	1.0
QALY excl. disutility (not discounted)	7.128	7.189	0.061	0.9
QALY excl. disutility (discounted)	6.257	6.307	0.050	0.8
Disutility due to complications	−0.016	−0.014	0.002	−12.5
Disutility due to history of complications	−0.032	−0.028	0.004	−12.5
Disutility due to baseline history of complications	−0.127	−0.128	−0.001	0.8
Total disutility due to complications	−0.175	−0.170	0.005	−2.9
Disutility due to diabetes medication use	−0.202	−0.112	0.090	−44.6
Disutility due to hypoglycemia	−0.068	−0.038	0.030	−44.1
Disutility due to excess BMI	−0.234	−0.198	0.036	−15.4
Total QALY (discounted)	5.579	5.789	0.211	3.8
Total QALY (not discounted)	6.353	6.601	0.247	3.9

BMI indicates body mass index; FMD, Fasting Mimicking Diet; QALY, quality-adjusted life year.

Table 3. Cost calculation for the diabetic population on dual and triple medications at baseline

Variable	Standard care	FMD	Difference in strategies	
			Absolute	Relative (%)
Costs due to complications	13 787	12 489	−1298	−9.4
Costs due to history of complications	4826	4392	−434	−9.0
Costs due to baseline history of complications	22 884	23 332	448	2.0
Costs due to cardiovascular mortality	5255	4638	−617	−11.7
Total costs due to complications	46 752	44 851	−1901	−4.1
Costs due to diabetes medications	76 929	30 315	−46 614	−60.6
Costs due to office visits	4837	4762	−75	−1.6
Costs due to self-management	1636	1183	−453	−27.7
Costs due to hypoglycemia	357	196	−161	−45.1
Total events costs	130 511	81 307	−49 204	−37.7
Costs of FMD program	-	7590	7590	NA
Total costs (discounted)	130 511	88 898	−41 613	−31.9
Total costs (not discounted)	149 335	99 688	−49 647	−33.2
All costs are in 2021 United States Dollars				

FMD indicates Fasting Mimicking Diet; NA, not applicable.

still need to add diabetes medications to control their glycemic level, despite the effect of FMD on HbA1c. Similar results were observed for the FMD-associated effectiveness benefit (Fig. 2).

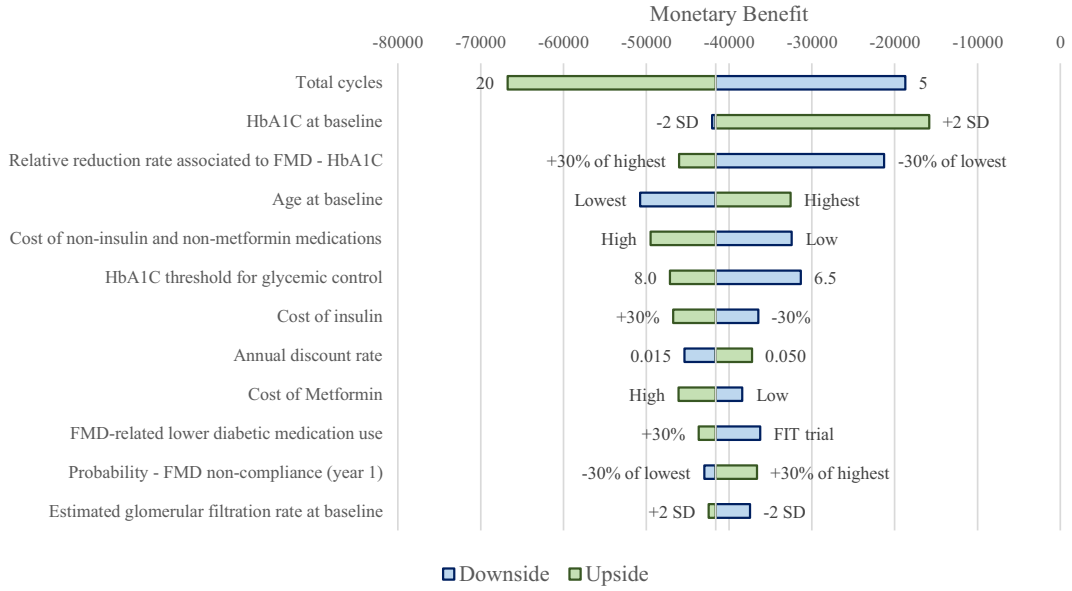
The PSA outcome showed a net distinction between FMD and the standard care on the cost-effectiveness scatterplot (Fig. 3). Indeed, the 10-year cumulative cost in the FMD simulated group was 89.5% below 106 000 USD (vs 0% in the simulated standard care group), and none was above 126 000 USD (vs 71.3%). Similar results were obtained for the 10-year cumulative effectiveness (Appendix Fig. 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.08.003). The PSA outcome also showed that 45.8% of the simulations generated a monetary benefit above 41 613 USD, and 50.5% generated an effectiveness benefit over 0.211 QALY (Supplemental Material found at https://doi.org/10.1016/j.jval.2024.08.003).

Discussion

According to the ADA, care for people with diagnosed diabetes accounts for 1 in 4 healthcare dollars in the United States.[2] Improving glycemic control is associated with improved adherence to medications[52] and reduced diabetes complications, comorbidities, and mortality.[53] Although most national diabetes associations and clinical practice guidelines recognize dietary interventions as essential in the management of T2DM,[54] there are few tools to connect patients with chronic illness to nutrition services from a healthcare system perspectives.[55]

Dietary interventions involving some form of fasting have emerged as potential therapeutic regimes for the prevention of a wide range of pathologies.[56] The FMD diet is a valuable complement to standard healthcare and could aid in sustaining health into advanced age.[14] The proof-of-concept study[26] and the FIT trial[27] demonstrated that FMD leads to significant improvement in metabolic parameters and reduction in the need for medication. It is widely believed that T2DM is a chronic progressive condition that requires indefinite and time-intensified treatment with glucose-lowering medications. These were reduced by 47% and 67% in patients in the FMD group in the FIT trial and the proof-of-concept study, respectively. Although they typically do not offer diabetes-specific counseling, widely available weight loss programs (such as Weight Watchers, Jenny Craig, Nutrisystem, or Slimfast) have shown to improve glycemic control. These programs were associated with 0.3 to 0.8 lower HbA1c level, 17% to 34% lower medication use, and 2% to 5% lower body weight at 3 to 12 months,[57,58] whereas a very-low-calorie diet-based program produced 1.3 lower HbA1c level, 48% lower medication use and 12% lower body weight at 1 year.[59] However, a significant rebound in HbA1c is often observed after the end of these programs,

Figure 1. Tornado diagram of most sensitive parameters affecting the monetary benefit (in 2021 USD) associated with the Fasting Mimicking Diet Negative values indicate cost savings. The monetary benefit was most sensitive to variation in the time horizon, certain patient' characteristics at baseline (glycated hemoglobin [HbA1c] level, age, and estimated glomerular filtration rate), assumptions on the benefits of Fasting Mimicking Diet program (HbA1c relative reduction rate, lower rate of diabetic medication use, and compliance rate), cost of diabetes medications, HbA1c threshold for glycemic control, and annual discount rate.



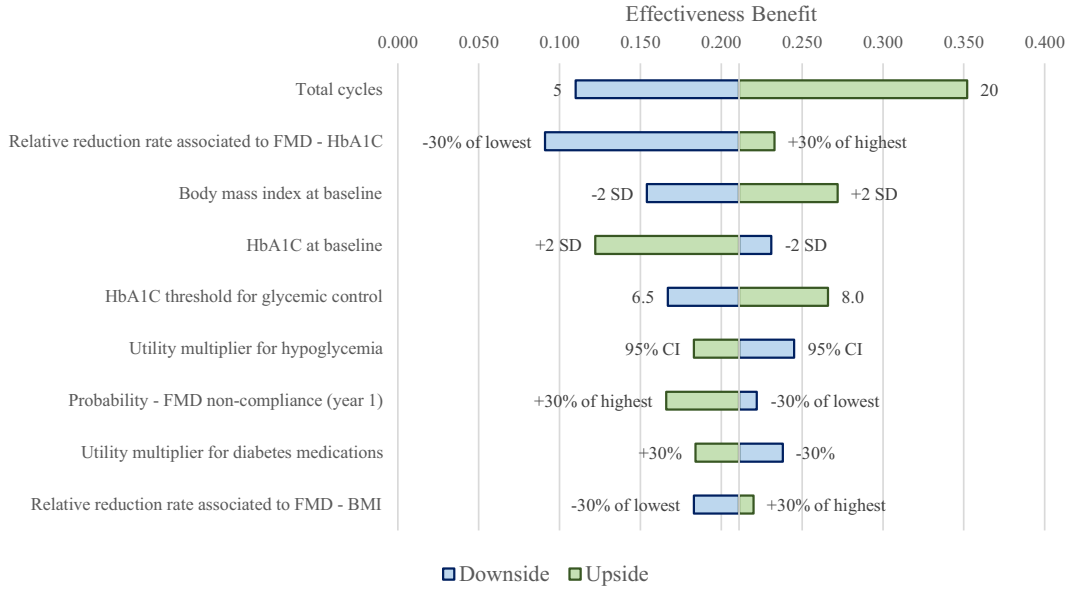
FMD indicates Fasting Mimicking Diet.

partially explained by the increase in caloric intake.[58] Long-term remissions are possible with a persistent change of lifestyle that includes changes in food intake among other actions that are associated with high burdens to patients.[60] The cyclic nature of the FMD is expected to increase compliance relative to traditional diets.[61] Moreover, a spin-off study from the FIT trial reported self-initiated behavioral improvements in both diet quality and physical activity in diabetic patients in the FMD group.[62] These results suggest the sustainability of FMD benefits on remission over time.

This cost-utility analysis is the first economic evaluation of the FMD nutri-technology, notably in a disease setting. It revealed that the FMD program in diabetic patients on dual and triple medications at baseline was associated with 11.4% less diabetes complications, 67.2% less overall diabetes medication use, and 45.0% less hypoglycemia events over the 10-year simulation period. The program generated an additional effectiveness benefit of 0.211 QALY and net monetary benefit of 41 613 USD per simulated patient. These gains were mainly driven by lower overall diabetes medication use in the simulated FMD group compared with the simulated standard care alone group. Because the program would cost less than the standard care, the FMD program is considered cost saving. The sensitivity analysis revealed that the monetary and effectiveness benefits were highly sensitive to variation in the time horizon and assumptions on the benefits of FMD program seen in trials. This warrants further studies to improve the certainty around these parameters. Our cost-utility analysis outcomes are on the conservative side as we adopted a restrictive time horizon of 10-year. Model outcomes' sensitivity to the time horizon is consistent with the nature of diabetes and lifestyle intervention modeling because longer time horizons are generally necessary to capture the development of key events and benefits and to reflect the overall value of the intervention.[38,63] Indeed, prolonging the time horizon to 20 years resulted in 60% higher net monetary benefit and 67% higher effectiveness benefit than with a 10-year time horizon. Our population analysis (Supplemental Material in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.08.003) demonstrated that simulated diabetic patients with more advanced disease (ie, on dual and triple medications at baseline) are expected to have greater benefits from integrating the FMD program to their standard care.

The current model has some limitations. We used available published information to describe the relationships between patient characteristics, health risk factors, and diabetes-associated events. Despite model complexity, the large number of parameters were taken from comparatively few studies, but from multiple sources. In particular, some sources collected data on a population outside the United States (ie, the UKPDS-OM2 or the FMD proof-of-concept study and FIT trial) or used relatively older data that may not represent the current standard of care (ie, the UKPDS-OM2, or the use of diabetes medications that may not fully capture the widespread use of some newer diabetes therapies and hence more expensive, such as glucagon-like peptide-1 receptors and sodium-glucose cotransporter-2 inhibitors). Although the UKPDS is widely used for economic evaluations of therapies for patients with T2DM, its reliability for contemporary diabetic populations, even in the United Kingdom, is unclear due to substantial changes in diabetes demographics (ie, younger age at diagnosis) and treatment (ie, earlier and aggressive management) since UKPDS was started.[30,64] Furthermore, our study was conducted from a private payer perspective in the US healthcare system (with generalizability to other healthcare systems may be limited), which defines the economic outcomes as direct medical expenditures. Numerous studies have established relationships between presence of diabetes, and lower productivity in the form of reduced employment, reduced earnings, absenteeism, and presenteeism.[43] Thus, our model does not estimate the social costs

Figure 2. Tornado diagram of most sensitive parameters affecting the effectiveness benefit associated with the Fasting Mimicking Diet program. The effectiveness benefit was most sensitive to variation in the time horizon, assumptions on the benefits of FMD program (glycated hemoglobin [HbA1c] relative reduction rate, compliance rate, and body mass index relative reduction rate), certain patient' characteristics at baseline (body mass index and HbA1c level), HbA1c threshold for glycemic control, and utility multipliers for hypoglycemia and diabetes medication use.

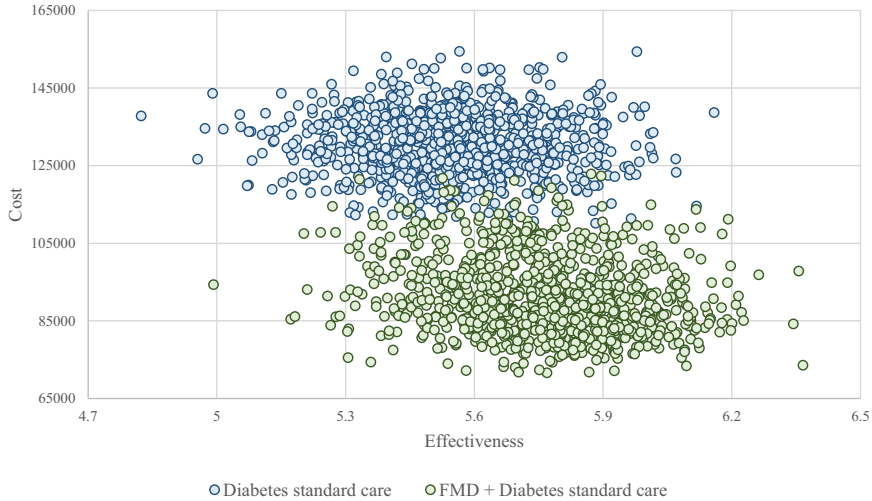


FMD indicates Fasting Mimicking Diet.

of diabetes. However, the results of the sensitivity analysis conducted on all major assumptions (including effectiveness of the FMD program, costs, and utilities) demonstrated the robustness of our conclusion on the FMD program cost-effectiveness.

In order for cost-utility analysis to be useful, it must include accurate information on all of the relevant costs and consequences of treatment. However, economic evaluation of lifestyle interventions is more complicated than that of the effect of a medication-based therapy, in which key health effects can be characterized in the short-term. This is because the lifestyle-associated weight loss can reduce risk for comorbidities of excess body weight beyond diabetes, such as cancer, cardiovascular disease, dementia, and other health issues.[38,43,65,66] We estimated only the monetary and effectiveness outcomes relating

Figure 3. Monte Carlo cost-effectiveness scatterplot. The TreeAge generated cost-effectiveness scatterplot shows the results of 1000 probabilistic sensitivity analysis simulations. A net distinction in the simulations between the Fasting Mimicking Diet and the standard care alone groups is observed.



FMD indicates Fasting Mimicking Diet.

to diabetes, whereas the FMD program may have beneficial effects on these other diseases, which would likely increase the benefits associated with the program. Consequently, the results of this cost-utility analysis are likely underestimated.

Conclusion

Trial results reported that integrating the FMD program is safe and feasible in adults with T2DM in real-world settings. This cost-utility analysis shows that the FMD diabetes program would represent good value for money in the United States. Our results, in addition to the reported clinical and behavioral findings, strongly support the addition of the FMD program as first-line strategy to T2DM management guidelines, allowing the possibility of diabetes regression to be within reach.

Author Disclosures

Author disclosure forms can be accessed below in the Supplemental Material section.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2024.08.003.

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