Case-based review

Abstract
- **Objective:** To provide a comprehensive review of the most recent recommendations for the use of medical nutrition therapy (MNT) in patients with diabetes.
- **Methods:** Review of the literature.
- **Results:** MNT is an effective adjunct therapy for individuals with diabetes and is associated with a 1% to 2% reduction in HbA1C. As weight loss is an integral component of the chronic management of type 2 diabetes, an energy-restricted diet is recommended. No optimal macronutrient distribution has been found to be efficacious for glycemic control or weight loss. A comprehensive program of lifestyle modification, comprised of diet, physical activity, and behavior therapy, induces a mean loss of 7% to 10% of initial weight in obese individuals with pre-diabetes or diabetes. Two trials demonstrated that weight loss of this magnitude, combined with increased physical activity, substantially reduced the risk of developing type 2 diabetes in individuals with impaired glucose tolerance. A third trial is now investigating whether a lifestyle intervention will reduce cardiovascular morbidity and mortality in overweight individuals who already have diabetes. Pharmacotherapy is recommended, in appropriate patients, as an adjunct to lifestyle modification. Two medications—oral regulatory and sibutramine—are currently approved in the United States for long-term weight loss. Both are efficacious when combined with lifestyle modification, although recent health concerns have been raised about sibutramine.
- **Conclusion:** To complement the medical management of diabetes, providers should be familiar with the underlying principles of MNT.

Given the impact of carbohydrates on glycemic control, dietary management remains the cornerstone of therapy for diabetes. Prior to the discovery of insulin in 1921, restricted food intake was the only method of regulating blood glucose levels. With the advent of rapid-acting insulin and the availability of many oral antidiabetic medications, nutrition recommendations have changed considerably over the past 15 years. Prior to the mid 1990s, patients were encouraged to follow an “ideal” nutrition prescription that included a prespecified percentage of calories and macronutrients. However, this approach was inflexible and did not allow for dietary individualization. In 1994, the American Dietetic Association introduced the term “medical nutrition therapy” to describe the process of providing individualized nutrition recommendations to patients that took their lifestyle and treatment goals into account [1].

Multiple randomized controlled trials have demonstrated the efficacy of medical nutrition therapy [2–5]. Medical nutrition therapy provided by a registered dietitian is associated with a 2.0% decrease in HbA1C in newly diagnosed type 2 diabetes [2] and a 1.0% decrease in newly diagnosed type 1 diabetes [3]. Although the greatest benefit has been shown at the time of diagnosis, multiple studies have demonstrated a sustained improvement in HbA1C at 12 months and longer [2,4,5]. Medical nutrition therapy also plays an important role in reducing cardiovascular risk factors, and has been found to decrease low-density lipoprotein (LDL) cholesterol by 15 to 25 mg/dL in nondiabetic individuals [6].

Although the effectiveness of medical nutrition therapy is well established, many patients may not have access to a dietitian. Despite national guidelines from expert health panels, including the American Diabetes Association (ADA) and the U.S. Preventive Services Task Force, rates of physician counseling and referral for nutrition and exercise among patients with diabetes remain poor [7–10]. In order to complement the medical management of diabetes, providers must become familiar with the underlying principles of medical nutrition therapy.

**CASE 1: AN OBESE WOMAN WITH TYPE 2 DIABETES**

A 43-year-old woman is referred to an endocrinologist for further evaluation of type 2 diabetes. She...
was recently diagnosed after her family physician noted that she had several fasting blood glucose measurements higher than 126 mg/dL. She has gained 25 lb over the past 2 years. She is currently taking metformin 1000 mg twice daily and is reluctant to take any additional medications. She has a history of dieting but has never seen a registered dietitian. She eats 3 meals a day and snacks between meals. She states that she has no time for physical activity due to her long work day and busy home life, but is willing to try dietary modification (with a goal of weight loss) before additional diabetes medications are added to her regimen.

On physical examination, she weighs 182 lb and stands 5' 1" tall. Her body mass index (BMI) is 34.4 kg/m². Her blood pressure is 128/84 mm Hg and her heart rate is 72 bpm. Her physical examination is notable for central adiposity but is otherwise unremarkable.

Laboratory testing reveals the following:

- Fasting glucose, 142 mg/dL (normal, 55–100 mg/dL)
- HbA1C, 7.3% (normal, 4.0%–6.0%)
- Total cholesterol, 204 mg/dL (normal, 140–199 mg/dL)
- Triglycerides, 167 mg/dL (normal, 35–150 mg/dL)
- Low-density lipoprotein (LDL) cholesterol, 120 mg/dL (normal, 50–129 mg/dL)
- High-density lipoprotein (HDL) cholesterol, 46 mg/dL (normal, 40–60 mg/dL)

### What are the benefits of weight loss in patients with diabetes?

Weight loss has been shown to confer the greatest benefit for individuals with pre-diabetes [11,12] or shortly after the onset of type 2 diabetes when insulin resistance is the predominant mechanism of impaired glycemia. As the disease progresses and insulin deficiency becomes more pronounced in the context of irreversible β cell dysfunction, weight loss has a more modest effect on glycemic control [13,14]. Bariatric surgery studies provide the most convincing evidence for this, as individuals with longstanding diabetes (> 10 years in duration) and insulin dependence are less likely to experience remission of diabetes, despite substantial weight loss [15]. Nonetheless, weight reduction remains a critical component in the treatment of longstanding type 2 diabetes, as it is associated with a significant reduction in the number of antidiabetic medications (many of which can promote weight gain), and has been shown to reduce cardiovascular risk factors [16–19]. A modest weight loss of 5% to 10% of body weight confers significant improvements in glycemic control, lipemia, and decreased blood pressure [18]. For every 4.5 kg loss in weight, HbA1C may be reduced by 0.5% [19]. Weight loss can be facilitated through behavioral treatments that promote lifestyle modification, as shown in Table 1.

### What lifestyle modifications are indicated and what is the evidence for efficacy of lifestyle intervention?

Lifestyle modification encompasses 3 core components: diet, physical activity, and behavior therapy [20]. Individuals are taught to achieve their food and activity goals by monitoring (keeping records of food intake and physical activity) or by modifying cues that elicit unwanted eating (stimulus control). Lifestyle modification is typically provided (to individuals or groups) on a weekly basis for 16 to 26 weeks. Group treatment has been shown to induce greater weight loss than individual therapy, and may be more cost effective [21]. Frequent self-monitoring is an essential component of a lifestyle modification program, and completion of daily food records is associated with greater initial weight loss [22]. Lifestyle modification programs typically induce a weight loss of 8% to 10% in the first 6 to 12 months, resulting in clinically
important health benefits [23]. However, most individuals regain one-third of the weight loss during the next year and return to their baseline weight within 3 to 5 years [24]. Weight regain can be minimized by frequent self-monitoring [25] as well as with ongoing face-to-face contact [26,27].

Several large clinical trials have provided strong evidence for the efficacy of lifestyle intervention for the prevention and treatment of type 2 diabetes [11,12,27]. In the Diabetes Prevention Program (DPP), over 3200 overweight individuals with impaired glucose tolerance were randomly assigned to either metformin, a lifestyle intervention designed to achieve a loss of 7% of initial body weight and increase physical activity, or placebo [11]. After an average treatment duration of 2.8 years, the lifestyle participants lost 5.6 kg, compared with losses of 2.1 kg and 0.1 kg in the metformin and placebo groups, respectively. Importantly, the risk of developing diabetes was decreased by 58% in the lifestyle group compared with placebo, and by 31% compared with metformin. Similar results were achieved in the Finnish Diabetes Study [12].

The Look AHEAD (Action for Health in Diabetes) study, a randomized controlled trial that includes 5145 overweight participants with type 2 diabetes, builds upon the results of the DPP. Look AHEAD was designed to assess whether weight reduction, in combination with increased physical activity, reduces cardiovascular morbidity and mortality in participants with type 2 diabetes [27]. Participants were randomized to either intensive lifestyle intervention (ILI), which includes group and individual meetings, or to a diabetes support and education (DSE) intervention. At the end of 12 months, participants assigned to ILI lost 8.6% of their initial weight, versus 0.7% in the DSE group (P < 0.001). Mean HbA1C decreased from 7.3% to 6.6% in the ILI group, versus 7.3% to 7.2% in the DSE condition. At 4 years, the ILI maintained a weight loss of 4.7% compared with a loss of 11% in the DSE group [28]. As Look AHEAD will be following participants for a mean of 13.5 years, it will provide important insight into the effects of long-term weight reduction on important clinical outcomes.

**Case 1 Continued**

The patient is referred to a registered dietitian for intensive nutrition counseling. Initially she is very motivated and records her food intake and activities daily. She loses 12 lb (7.0% weight loss) over the next 3 months. Her HbA1C decreases by 0.7% and her lipid profile improves. However, she tires of daily monitoring and stops recording her food intake. Over the next month, she regains 5 lb. She meets with the dietitian again, who re-engages her and recognizes that she needs more support. As her insurance will not allow her to meet monthly with the dietitian, they decide to communicate weekly via electronic mail to monitor her progress. During her appointment with the endocrinologist, she also asks about weight loss medication.

- **What are the options for pharmacotherapy for weight loss and what is the evidence in individuals with diabetes?**

In order to maximize initial weight loss and minimize weight regain, drug therapy can be used in combination with continued lifestyle modification. According to the National Institutes of Health guidelines for the treatment of obesity, pharmacotherapy is indicated for individuals with a BMI ≥ 30 kg/m² (or ≥ 27 kg/m² with comorbidities) [29]. Currently, only sibutramine and orlistat are approved by the U.S. Food and Drug Administration for long-term use in the treatment of obesity. Several other medications are commonly used “off-label” for the treatment of obesity [30–45] and are listed in Table 2.

**Sibutramine**

Sibutramine (Meridia), a centrally acting appetite suppressant that inhibits serotonin and norepinephrine reuptake, has been found to be efficacious in individuals with type 2 diabetes. The dose of sibutramine is 5 to 10 mg/day, although it may be increased to 15 mg/day in patients who do not achieve a more than 2-kg weight loss after 4 weeks of treatment [46]. In a recent Cochrane systematic review [32], the pooled estimate for placebo-subtracted weight loss with sibutramine (for 8 randomized controlled trials that included 1047 participants with diabetes) was 5.1 kg (95% confidence interval [CI], 3.2 to 7.0). Mean reduction in HbA1C was 0.5% (95% CI, −0.2 to 1.3).

Common side effects of sibutramine include increased blood pressure and pulse, palpitations, dry mouth, insomnia, and constipation [32]. Sibutramine is contraindicated in persons with existing cardiovascular disease (prior coronary artery disease, stroke, or transient ischemic attack), cardiac arrhythmias, congestive heart failure, peripheral arterial disease, and uncontrolled hypertension (ie, >145/90 mm Hg). This was further underscored by preliminary data analysis from the ongoing Sibutramine Cardiovascular OUTcomes (SCOUT) trial, a large randomized study designed to assess the safety of sibutramine in individuals with existing cardiovascular disease, hypertension, or diabetes [47]. A higher rate of cardiovascular events was observed in the sibutramine group compared to placebo (11.4% vs. 10%), although the increased risk occurred only in participants who had a prior history of cardiovascular disease [48]. Sibutramine remains available in the United States, but it was withdrawn from the European market in January 2010 amid safety concerns [49].
MediCal NuTriTiON THeraPY

Orlistat
In contrast to the central effects of sibutramine, orlistat (Xenical) reduces fat absorption by locally inhibiting pancreatic lipase [30]. The dose of orlistat is 120 mg three times daily, although it is also available over the counter (Alli) in a 60-mg dose. Orlistat is associated with mainly gastrointestinal side effects, as described in Table 2. The pooled estimate for placebo-subtracted weight loss with orlistat (from

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose and Dosing Recommendations</th>
<th>Average Associated Weight Loss, kg</th>
<th>Side Effects</th>
<th>Absolute and Relative Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serotonergic reuptake inhibitors</strong></td>
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<tr>
<td>Sibutramine*</td>
<td>5, 10, or 15 mg once daily (recommend taking in the morning to avoid insomnia)</td>
<td>−4.5 to 5.1 [32,33]</td>
<td>Increased blood pressure and heart rate Palpitations Insomnia Nausea Dry mouth Constipation</td>
<td>History of cardio- or cerebrovascular disease Arrhythmia Peripheral arterial disease Concurrent use of the following medications: Selective serotonin reuptake inhibitors Monoamine oxidase inhibitors Triptans</td>
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<td><strong>Lipase inhibitors</strong></td>
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<tr>
<td>Orlistat*</td>
<td>120 mg three times daily with meals (also available OTC in 60-mg dose as Alli). Recommend restricting fat intake to less than 30% of calories from fat throughout the day and less than 15 g per meal. Also recommend taking a daily multivitamin containing fat-soluble vitamins at least 2 hours before or after orlistat [35].</td>
<td>−2.0 to −2.6 [32,36]</td>
<td>Fatty and oily stool Fecal urgency Fecal incontinence Decreased absorption of fat-soluble vitamins</td>
<td>Can reduce the absorption of amiodarone, levothyroxine, and cyclosporine and can potentiate effect of warfarin (use with caution in patients taking these medications)</td>
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<td><strong>Adrenergic agents</strong></td>
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<tr>
<td>Phentermine†</td>
<td>15, 30, 37.5 mg once daily</td>
<td>−6.4 [38]</td>
<td>Increased blood pressure Tachycardia Palpitations Insomnia</td>
<td>Cardiovascular disease Uncontrolled hypertension Hyperthyroidism</td>
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<tr>
<td><strong>Selective serotonin reuptake inhibitors (SSRIs)</strong></td>
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<tr>
<td>Fluoxetine</td>
<td>10, 20, 40 mg once daily (recommend taking in the morning to avoid insomnia)</td>
<td>−3.4 to −5.8 [32,36]</td>
<td>Insomnia Sweating Dry mouth Constipation</td>
<td>Concurrent use of monoamine oxidase inhibitors Concurrent use of sibutramine</td>
</tr>
<tr>
<td><strong>Antiepileptic medications</strong></td>
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<tr>
<td>Topiramate</td>
<td>175–200 mg daily (dose used in clinical trials for weight loss)</td>
<td>−6.0 to −6.4 [39,40]</td>
<td>Paresthesias Headache Somnolence Difficulty with memory and concentration Constipation</td>
<td>Glaucoma</td>
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</tbody>
</table>

(Table continued on next page)
8 randomized controlled trials that included 2036 participants with diabetes) was 2.0 kg (95% CI, 1.3 to 2.8) with a mean reduction in HbA1C of 0.5% (95% CI, 0.3 to 0.6) [32].

**Evidence from Clinical Trials**

The importance of prescribing weight loss medication in conjunction with lifestyle modification is underscored by a 1-year trial that randomly assigned nondiabetic participants to 1 of 4 treatments: (1) sibutramine 15 mg alone, (2) lifestyle counseling alone, (3) sibutramine in combination with brief counseling (8 visits delivered by a primary care provider in 10–15 minutes), or (4) sibutramine in combination with intensive lifestyle counseling (combined therapy) [22]. Participants in the combination group lost twice as much weight (12 kg) compared with the group that received sibutramine alone (5.0 kg) or lifestyle modification alone (6.7 kg). Subsequent studies performed in participants with metabolic syndrome and diabetes reported greater weight loss with combination therapy [50,51]. Participants in the combination group lost twice as much weight (12 kg) compared with the group that received sibutramine alone (5.0 kg) or lifestyle modification alone (6.7 kg). Subsequent studies performed in participants with metabolic syndrome and diabetes reported greater weight loss with combination therapy [50,51]. Participants in the combination group lost twice as much weight (12 kg) compared with the group that received sibutramine alone (5.0 kg) or lifestyle modification alone (6.7 kg). Subsequent studies performed in participants with metabolic syndrome and diabetes reported greater weight loss with combination therapy [50,51]. Participants in the combination group lost twice as much weight (12 kg) compared with the group that received sibutramine alone (5.0 kg) or lifestyle modification alone (6.7 kg). Subsequent studies performed in participants with metabolic syndrome and diabetes reported greater weight loss with combination therapy [50,51].

**Lifestyle modification (and pharmacotherapy) can be also combined with other dietary approaches to elicit greater initial weight losses.”**

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**Table 2. (continued)**

<table>
<thead>
<tr>
<th>Drug</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidiabetic medications</strong></td>
<td></td>
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<tr>
<td>Metformin</td>
<td>500, 850, 1000 mg once to twice daily</td>
<td>−1.5 [11]</td>
<td>Nausea Abdominal pain Loose stools or diarrhea</td>
<td>Concurrent use of monoamine oxidase inhibitors</td>
</tr>
<tr>
<td>Acarbose</td>
<td>25 mg with meals</td>
<td>−1.1 to −1.5 [41,42]</td>
<td>Diarrhea Abdominal pain Flatulence</td>
<td>Renal impairment (not recommended if serum creatinine &gt; 2.0 mg/dL)</td>
</tr>
<tr>
<td>Exenatide</td>
<td>5 to 10 mcg twice daily</td>
<td>−2.8 [43]</td>
<td>Nausea Hypoglycemia Insomnia Nausea Dry mouth Constipation</td>
<td>Use with caution in combination with glucose-lowering agents and/or insulin</td>
</tr>
<tr>
<td>Pramlintide</td>
<td>120 mcg twice daily</td>
<td>−1.0 to 1.4 [44,45]</td>
<td>Nausea Hypoglycemia (especially in patients treated concurrently with insulin)</td>
<td>Use with caution in combination with glucose-lowering agents and/or insulin</td>
</tr>
</tbody>
</table>

Adapted from reference 30.

*Approved for long-term use [31,34].
†Approved for short-term use (less than 12 weeks) [37].

• What are guidelines for carbohydrate intake in diabetes management?

The glycemic response is determined not only by the amount of carbohydrate but also by the type of carbohydrate. Carbohydrates are classified as sugars (monosaccharides and disaccharides), sugar alcohols, fiber, and other carbohydrates (oligosaccharides and starches) [52]. In addition to the type of carbohydrate, the physical properties of the food, the viscosity, and other dietary factors affect glycemic response [53]. Medical nutrition therapy emphasizes the total carbohydrate content of a meal rather than the individual types of carbohydrates [54].

**Effect of Different Types of Carbohydrates on Glycemia**

Sugars are absorbed, digested, and fully metabolized, and include monosaccharides (glucose, fructose, and galactose) and disaccharides (sucrose, maltose, and lactose) [52]. Several randomized trials have found no difference in glycemia in participants with type 1 or 2 diabetes when sucrose is
substituted for equal amounts of other types of carbohydrates [53–58]. Thus, sucrose and other sugars can be incorporated into meals, as long as they are substituted for other sources of carbohydrates [54]. High-fructose corn syrup, which is used in many foods and contains 50% fructose and 50% glucose, has been more controversial. Studies have yielded inconsistent findings on whether high-fructose corn syrup has adverse effects on glycemic control [52]. Paradoxically, fructose is associated with a lower postprandial glycemic response [52]. Sugar alcohols (also known as polyols) are used to fully or partially replace added sugars in foods and include the alcohol forms of mono- and disaccharides [52]. Sugar alcohols induce significantly lower postprandial glycemic responses than fructose, sucrose, or glucose in individuals with diabetes.

Dietary fiber is not digested and therefore does not contribute to the immediate glucose supply. Dietary fiber is classified as either soluble or insoluble and is associated with reduced postprandial excursions of both glucose and triglycerides [59]. Soluble fibers are derived from whole grain products and fruit (pectin) and are fermented in the colon [60]. In contrast, insoluble fiber (including wheat bran) has bulking action and is only fermented to a limited extent in the colon. The 2 classes of fiber have different effects on glycemia. Soluble fiber delays the digestion and absorption of carbohydrates, thus reducing insulin requirements [61]. Insoluble fiber may improve glycemia by decreasing the production of short chain fatty acids in the colon, which affects hepatic insulin sensitivity [62].

Several randomized controlled trials have evaluated the effect of varying the amount of dietary fiber (while controlling the total amount of dietary carbohydrate) on glycemic control in both type 1 and type 2 diabetic participants. While there was no difference in HbA1C between high- and low-fiber diets, postprandial blood sugars were lower in participants who followed a high-fiber diet. Chandalia and colleagues, in a randomized crossover study that compared a diet of moderate fiber content (24 g) to a high-fiber diet (50 g), found that the high-fiber diet was associated with lower preprandial and 24-hour glucose concentrations [63]. Additionally, plasma total cholesterol concentrations and triglycerides were reduced by 5.7% and 10.2%, respectively. The ADA recommends that individuals with diabetes consume a similar amount of dietary fiber to that recommended by the American Dietetic Association for all U.S. adults (20–35 g daily) [64]. According to the most recent NHANES data, the average dietary fiber intake for U.S. adults was 15 g [65].

Options for Managing Carbohydrate Intake
Carbohydrate intake may be monitored by carbohydrate counting, exchanges, or experience-based estimation [54]. The Diabetes Control and Complications Trial (DCCT) firmly established carbohydrate counting as an integral component of management for type 1 diabetics [66]. However, its efficacy is less established in type 2 diabetics. Several studies suggest that patients prefer other strategies in lieu of carbohydrate counting [67,68].

- Is there an optimal macronutrient distribution for achieving weight loss and improved glycemic control? What is the evidence for different types of diets among individuals with diabetes?

The optimal macronutrient composition of weight loss diets has not been established [54]. Sacks and colleagues found, in a 2-year randomized trial that compared isocaloric diets of varying macronutrient composition, that weight loss was similar (regardless of the distribution of macronutrients) [69]. Similarly, Dansinger and colleagues [70] suggested that the optimal diet is the one to which individuals have the best adherence. An energy-reduced diet should be recommended for weight loss. Individualization of the macronutrient composition will depend on the metabolic status of the patient (eg, lipid profile and renal function) and/or food preferences [71]. General recommendations for macronutrient composition are provided in Table 3.

Low-Carbohydrate Diets
As carbohydrates are the main determinant of postprandial glycemia, there is continued interest in low-carbohydrate diets as a treatment for diabetes. However, carbohydrate restriction remains controversial, given the fact that carbohydrate is often replaced by fat (particularly saturated fat), which may have adverse effects on cardiovascular outcomes and glycemic control [72,73]. Although there are no standard criteria, low-carbohydrate diets typically contain between 50 and 100 g of carbohydrate daily [74,75]. Ketosis rarely occurs when carbohydrate intake is greater than 50 g [76]. Most low-carbohydrate diets allow unrestricted fat and calories, although unsaturated fats are emphasized rather than saturated or trans fats [75]. While the ADA does not recommend or advise against carbohydrate restriction, the most recent guidelines state “low-carbohydrate and low-fat diets may be effective for short-term weight loss (up to 1 year)” [71]. Although central nervous system glucose demands can be met with a carbohydrate intake below the recommended daily allowance of 130 g/day [54], the ADA cautions that such diets eliminate many foods that are important sources of energy, fiber, vitamins and minerals [71]. An energy-restricted diet containing healthy carbohydrate foods may be preferable. Additionally, the ADA recommends that lipid profiles, renal function, and protein intake (in those patients
Evidence for Low-Carbohydrate Diets

Low-carbohydrate diets are associated with rapid weight loss, in both diabetic and nondiabetic individuals [16,77–82]. A recent meta-analysis of 13 studies of carbohydrate-restricted diets in type 2 diabetics reported significant reductions in HbA1C and triglycerides in participants randomized to low-carbohydrate diets ($P = 0.013$ and $P < 0.001$, respectively) compared with low-fat diets [80]. However, the studies included in the meta-analysis were short in duration, ranging from 2 weeks to 26 weeks. Longer-duration studies (up to 12 months) have consistently shown that weight loss is not maintained in the low-carbohydrate group, and by 12 months, weight change is equivocal between dietary groups [81–83]. Moreover, multiple long-term studies (duration from 1 to 2 years) have found no significant differences in glycemic control, LDL cholesterol,
or blood pressure between diabetic individuals who followed a low-carbohydrate diet and those who followed a low-fat or low-glycemic diet [83–85].

Until recently, few studies evaluated the long-term efficacy of carbohydrate restriction. Shai and colleagues [86] reported superior weight loss in a 2-year randomized controlled trial among 322 obese participants assigned to a low-carbohydrate, Mediterranean, or low-fat diet. Mean weight losses at 2 years were 4.7 kg, 4.4 kg, and 2.9 kg, respectively (P < 0.001 for both comparisons with the low-fat group). In the subsample of 36 diabetic participants, HbA1C decreased significantly by 0.9% in the low-carbohydrate group (P < 0.05 compared with the other 2 groups), although the study was underpowered to detect significant changes in the diabetic participants. A recent follow-up study of a randomized controlled trial of low-carbohydrate versus low-fat diets evaluated weight and metabolic parameters in 132 participants with a high prevalence of diabetes or the metabolic syndrome at 36 months (2 years after completion of the 12-month dietary intervention) [87]. At 36 months, weight change from baseline did not differ significantly between the groups (–2.2 kg in the low-carbohydrate group and –4.3 kg in the low-fat group; P = 0.343). Greater weight loss from baseline to 12 months was associated with greater weight regain by 36 months. Importantly, carbohydrate restriction during the first 12 months did not cause detrimental effects on lipid levels or renal function at any time during the subsequent 36 months. By 36 months, dietary intake for both groups reverted to baseline patterns.

Low-Glycemic Diets

As previously discussed, both the relative amount and the type of carbohydrate influence the glycemic response to food [53]. The glycemic index (GI) was developed to compare the postprandial response to standardized amounts of different carbohydrates. The GI is defined as the incremental area under the blood glucose response curve after consumption of 50 g of a test food relative to 50 g of a reference food (usually white bread or glucose) [88]. The glycemic load of a meal is calculated by multiplying the glycemic index of the individual foods by the amount of carbohydrate, and then adding up the values for all of the foods. High-glycemic foods, such as highly processed, starchy foods, induce postprandial hyperglycemia and associated hyperinsulinemia [89]. Low-glycemic index foods, such as lentils, beans, oats, and nonstarchy vegetables, are associated with lower postprandial blood sugars and lower insulin levels.

Evidence for Low-Glycemic Diets

Thomas and Elliot found, in a recent Cochrane review that included 402 type 1 and 2 diabetic participants, significant improvements in glycemic control on a low-glycemic index diet as compared with a higher glycemic index diet [90]. Low glycemic diets were associated with a decrease of 0.5% in HbA1C. Additionally, low-glycemic diets have been associated with significant improvements in insulin sensitivity, as measured by the hyperinsulinemic euglycemic clamp [91]. However, most of the studies included in the systematic review were short-term, ranging from 4 to 6 months, and included small numbers of participants. More recently, Jenkins and colleagues [92] found, in a 6-month randomized controlled trial that compared a low-glycemic index diet and a high-fiber cereal diet among 210 diabetic participants, that HbA1C was significantly decreased in the low-glycemic group compared with the high-cereal fiber group (–0.5% vs. –0.2%; P < 0.001). High-density lipoprotein cholesterol also increased in the low-glycemic index group, whereas it decreased in the high-cereal fiber group (P = 0.005). Two longer-term studies found no difference in weight loss or HbA1C at 12 months between diabetic participants assigned to a low-glycemic diet versus an ADA diet [93], or to diets of varying carbohydrate content [83].

Mediterranean Diet

As many studies have demonstrated that a Mediterranean diet pattern has beneficial effects on cardiovascular health [94–97], recent research has focused on its effect on diabetes. Mediterranean diets emphasize the moderate consumption of fats (30%–40% of daily energy intake, primarily from MUFAs such as olive oil), fruits, vegetables, nuts, whole grains, fish, and moderate consumption of wine. Several recent large trials have examined its effect on glycemic indices and insulin sensitivity [98–100].

Estruch and colleagues [100] found, in a subgroup analysis of 772 participants at high risk for cardiovascular disease (including those with type 2 diabetes) in the PREMID study, that a Mediterranean diet was associated with greater reduction of lipid levels, insulin resistance, blood pressure, and inflammatory markers as compared with a low-fat diet. However, this study was limited by a short duration of follow-up (3 months). Recent long-term data have been promising. Brehm and colleagues [94] found, in a 1-year randomized trial of 124 overweight and obese diabetic participants, that metabolic improvements were similar in those who followed a Mediterranean diet versus a high-carbohydrate diet. In a 2-year randomized controlled trial, Shai and colleagues [86] reported greater decreases in fasting glucose levels in the subsample of diabetic participants who followed a Mediterranean diet as compared with those who followed a low-carbohydrate or low-fat diet. Additionally, the homeostasis model assessment-insulin resistance (HOMA-IR) was also significantly lower in the Mediterranean group. As per the most recent ADA guidelines on nutrition, a Mediterranean diet is an also acceptable dietary option for the management of diabetes [54].
Other Diets

Vegetarian and vegan diets may also have beneficial effects on weight loss and glycemic control. Barnard and colleagues [101] reported a significant reduction in HbA1C, total and LDL cholesterol, and triglycerides in diabetic participants randomly assigned to a low-fat vegan diet for 74 weeks compared with those who followed a conventional diabetic diet.

- In addition to affecting cardiovascular risk, does dietary fat quality affect insulin action?

Dietary Fat in Diabetes Management

Given the association between dietary fat intake and lipemia, the type of fat consumed plays an important role in cardiovascular risk reduction. Fat quality may also affect insulin sensitivity via alterations in cell membrane composition, lipogenic gene expression, and enzyme activity [102].

Effects of Specific Types of Fat on Cardiovascular Risk Factors and Insulin Sensitivity

Saturated fatty acids. Saturated fatty acids, which are found predominantly in animal products, are one of the principal determinants of LDL cholesterol. Given the known association of saturated fats and cardiovascular disease in non-diabetic individuals, the ADA currently recommends that saturated fat intake be restricted to < 7% of total energy [54]. Saturated fats have been found to decrease insulin sensitivity [78,79]. In conjunction with the restriction on saturated fat, the ADA also recommends limiting dietary cholesterol to < 200 mg/day [54].

Trans fatty acids. Trans fats are formed during the process that converts vegetable oils into semisolid fats for use in margarines, commercial cooking, and manufacturing processes [103]. Trans fats have been shown to increase both LDL cholesterol and triglycerides, and reduce levels of HDL cholesterol [104]. In addition to inducing an atherogenic dyslipidemia, trans fatty acids may also promote inflammatory cytokines and induce endothelial dysfunction. Even a low consumption of trans fats (1%-3% of total caloric intake) appears to substantially increase the risk of CHD [103,105,106]. Few studies have examined the effects of trans fatty acid on insulin sensitivity, although there appears to be an association between higher trans fat intake and diabetes. Recent animal studies suggest that trans fatty acids may impair adipocyte membrane fluidity and insulin sensitivity, possibly through downregulation of PPAR-γ in adipose tissue [107]. The ADA currently recommends minimal intake of trans fatty acids [54].

Polyunsaturated fatty acids. Polyunsaturated fatty acids (PUFAs) have more than 1 double bond (which allows them to remain as liquids at low temperatures). The ω-3 fatty acids include fish oil and α-linolenic acid, which is found in canola oil. A systematic review that included 23 randomized controlled trials of ω-3 supplementation with a mean of 3.5 g/d in a total of 1075 participants with diabetes found significant reductions in triglyceride levels (–0.45 mmol/L; P < 0.001) and HDL cholesterol (–0.07 mmol/L; P = 0.04) [108]. Although LDL cholesterol increased slightly with ω-3 supplementation, the increase was nonsignificant in subgroup analysis. Omega-3 supplementation did not have any effect on fasting glucose, insulin, or HbA1C.

Omega-6 fatty acids. Omega-6 fatty acids, which are found in vegetable oils, also reduce cardiovascular risk. Linolenic acid is the most common ω-6 PUFA. In the Nurses’ Health Study, a greater intake of linoleic acid (up to 8% of energy intake) was related to a lower risk of myocardial infarction or CHD death [106]. In contrast to the ω-3 PUFAs, ω-6 PUFAs appear to affect insulin sensitivity. A recent randomized controlled crossover study that included more than 50% obese or diabetic participants found that an ω-6 PUFA-rich diet improved insulin sensitivity (as assessed by a euglycemic clamp) within 5 weeks as compared with a diet that was high in saturated fat [91]. The ω-6 fatty acids are thought to decrease insulin resistance by acting as a ligand for peroxisome proliferators-activated receptors [109]. Intake has been inversely related to the risk of type 2 diabetes [106].

Monounsaturated fatty acids. Oleic acid, which is contained in olive oil, is the predominant source of monounsaturated fatty acids (MUFAs) in many diets. A recent meta-analysis found that high-MUFA intake improved fasting glucose, triglyceride, total cholesterol, and HDL cholesterol levels, but not HbA1C or LDL cholesterol concentrations [110]. Brehm and colleagues found, in a 12-month randomized trial that compared a diet high in MUFA and a high-carbohydrate diet in 124 overweight/obese participants with type 2 diabetes, that both groups lost a similar amount of weight (–4.0 kg vs. –3.8 kg) and had comparable improvements in HbA1C, fasting glucose, body fat, and waist circumference [94]. In a subset of participants (n = 36) followed at 18 months, decreased weight and improvements in HbA1C were maintained.

- What other nutrition supplementation is recommended?

Chromium

Chromium is thought to be a cofactor necessary for optimal
insulin action and has generated considerable interest among the public as a possible treatment for insulin resistance. Although it is available in several preparations, chromium picolinate is the most readily absorbed. Studies of the effect of chromium supplementation on glycemia have been inconsistent [111–114]. A recent systematic review that included 41 studies (a total of 1198 participants with and without diabetes) found no significant effect of chromium supplementation on lipid or glucose metabolism in individuals without diabetes [115]. However, chromium picolinate was found to decrease HbA1C by 0.6% and fasting glucose by 1.0 mmol/L in people with diabetes. Given the poor quality and significant heterogeneity of the included studies, the authors suggested that chromium may have a modest benefit on glycemia and dyslipidemia in individuals with diabetes. As the evidence for chromium supplementation remains inconclusive, the ADA currently does not recommend its use [54].

Antioxidants and Other Supplements

As oxidative stress appears to be involved in the pathogenesis of both cardiovascular disease and diabetes [116], the protective role of antioxidants has garnered considerable interest. Few studies have examined the role of antioxidants in diabetic participants, and results have been inconsistent. While Milman and colleagues [117] reported a significant reduction in cardiovascular events in 1434 diabetic individuals randomly assigned to 400 U/day of vitamin E, other studies have shown no benefit [118] and possibly harm [119]. Studies of vitamin C supplementation in individuals with diabetes also have yielded inconsistent results [120,121], although there is no evidence of harm. Evidence for herbal supplements and other trace minerals also remains sparse. In a systematic review that included 108 trials of 4565 participants with diabetes or impaired glucose tolerance, Yeh and colleagues [122] found insufficient evidence to support the efficacy of individual herbs and supplements for glycemic control. Given the lack of clear evidence and the fact that a balanced diet provides adequate levels of essential vitamins and minerals, both the ADA and the American Heart Association [54,123] recommend against routine supplementation of antioxidants or the use of herbal products.

Case Conclusion

With the ongoing support of the dietitian and the endocrinologist, the patient continues to follow a Mediterranean-style diet. She has also been taking orlistat. At the end of 1 year, she has successfully maintained a weight loss of 15 lb (8.0% of body weight). Her HbA1C has decreased to 6.4%, and her triglycerides and LDL cholesterol levels are now 120 mg/dL and 109 mg/dL, respectively.

CASE 2: THE TUBE-FED PATIENT

A 75-year-old man with type 2 diabetes is admitted to the hospital after sustaining a large left hemisphere stroke. He previously had good glycemic control on a regimen that included metformin 1000 mg twice daily, pioglitazone 30 mg once daily, and repaglinide 2 mg three times daily. His oral antidiabetic medications have been discontinued since he was admitted to the hospital and he is currently receiving sliding scale insulin. His nutrition regimen consists of continuous tube feeds with a standard formula at 50 cc/hr. He has been persistently hyperglycemic to the mid-200 mg/dL range.

- What are general principles of inpatient medical nutrition therapy for diabetes?

Recently the guidelines for inpatient glycemic targets were revised. Current ADA and American Association of Clinical Endocrinologists (AACE) guidelines recommend a target blood glucose level of 140 to < 180 mg/dL for critically ill patients, and 100 to 180 mg/dL for most patients admitted to general medical or surgical wards [124]. As hyperglycemia is common in hospitalized patients as a consequence of acute illness, iatrogenic causes, and other factors, medical nutrition therapy is an integral component in optimizing glucose control.

Evidence for the optimal diet for hospitalized patients with diabetes remains lacking. Although many hospitals continue to use calorie-specific diets, the total daily grams of carbohydrate are now emphasized [125]. The carbohydrate amount should be consistent from meal to meal and from day to day [126]. “Carbohydrate-controlled” diets in the hospital setting typically provide between 1800 to 2000 calories and contain 180 to 225 grams of carbohydrates to be distributed throughout the day. Patients who are consuming a clear or full liquid diet should also have a consistent amount of carbohydrates. To prevent starvation ketosis, roughly 200 grams of carbohydrate should be provided throughout the day [127].

- What would be an appropriate enteral formula for this patient and how can his insulin management be improved?

Enteral Nutrition

Hyperglycemia, which occurs in up to one-third of adult patients who receive enteral nutrition [128], is associated with poor clinical outcomes, increased infection rates [129],
and increased mortality in hospitalized patients [130]. Caloric goals should be determined by predictive or simplistic formulas or indirect calorimetry under the guidance of a registered dietitian to minimize the risk of overfeeding [54]. Standard formulas, which are typically high in carbohydrate and low in both fat and fiber, are commonly implicated in the development of hyperglycemia. In contrast, diabetes-specific formulas are typically higher in fat (40%–50% of calories), lower in carbohydrate content (35%–40% of calories), and contain up to 15% fructose [131]. Diabetes-specific formulas are also frequently enriched with ω-3 polyunsaturated fatty acids, chromium, and antioxidants [132]. These nutrients may improve glycemic control by delaying gastric emptying (as a result of increased fat and fiber), delaying the intestinal absorption (fiber), and the production of smaller glycemc responses (fructose). A recent meta-analysis that included 784 patients from 23 short-term studies of low to moderate quality found that diabetes-specific formulas significantly reduced postprandial rise in blood glucose, peak blood glucose concentration, and glucose area under the curve as compared with standard formulas [131]. The improved glycemic control was achieved without evidence of hypoglycemia. Additionally, individual studies reported a decreased requirement for insulin (26%–71% lower) and fewer complications with diabetes-specific formulas. A recent long-term randomized controlled trial that compared a diabetes-specific formula with a standard formula in tube-fed, insulin-treated patients with type 2 diabetes reported similar results [132].

Although several studies have shown that a basal-bolus insulin regimen results in better glycemic control in hospitalized patients with diabetes than sliding-scale regular insulin, very few studies have specifically evaluated optimal strategies to manage hyperglycemia in those who require enteral feedings [133,134]. A recent randomized trial compared subcutaneous insulin regimens in non-critically ill patients with hyperglycemia who received enteral nutrition [134]. Fifty patients (including those with and without diabetes) with hyperglycemia, defined as more than 2 blood glucose concentrations > 130 mg/dl, were randomly assigned to receive sliding scale insulin plus glargine once daily (n = 25) or sliding scale insulin alone (n = 25). NPH was added if patients remained persistently hyperglycemic in the sliding scale group. Mean daily blood glucose values were similar between the groups, and the frequency of hypoglycemia did not differ. However, more than two-thirds of the patients with diabetes required the addition of NPH insulin, underscoring the importance of adding basal insulin to a sliding scale insulin regimen for patients with diabetes or persistent hyperglycemia.

Several options exist for prandial insulin coverage for patients who receive enteral nutrition support. For continuous feedings, insulin may be administered every 4 to 6 hours, with the expected carbohydrate intake matched to the duration of action of the type of insulin used [135]. Regular insulin is typically used for continuous enteral feedings. Rapid-acting insulin or regular insulin may be used for bolus and intermittent feedings and should be administered immediately after the feedings. Correction insulin should be used to treat hyperglycemia that occurs despite basal and prandial coverage. As tube feedings are frequently interrupted, hypoglycemia may occur. Dextrose can be administered to compensate for the missed carbohydrate when feedings are interrupted, or in cases where prandial insulin was administered prior to the discontinuation of tube feeding [135].

**Total Parenteral Nutrition**

Patients who require total parenteral nutrition (TPN) are particularly susceptible to hyperglycemia, as the formulas contain a high glucose content and the patients are often critically ill. Additionally, TPN is administered intravenously and bypasses the gut, thereby eliminating the incretin contribution to insulin secretion [136]. Thus, insulin needs are often higher for patients receiving TPN compared with those who are tube-fed. Regular insulin may be added to the TPN bag and should be used to cover only the dextrose in the formula [135]. Typically 1 unit of insulin is added for every 10 g carbohydrate, although the insulin to carbohydrate ratio can vary considerably among patients [136]. The addition of insulin to the bag decreases the risk of hypoglycemia, as insulin delivery is stopped if the TPN is discontinued. Basal insulin should be added independently, either via an insulin drip or using a long-acting insulin [135]. More prospective randomized studies are needed to determine the optimal management of hyperglycemia in patients who receive nutrition support.

**Case Conclusion**

The patient’s tube feeding is changed from a standard formula to a diabetes-specific formula, and the volume is increased to provide adequate calories and nutrition to prevent weight loss. Glucerna 1.2 is ordered at 62.5 cc/hour to deliver 1800 cal, 171.8 g of carbohydrate, 90 g of protein, and 25 g of fiber. As the enteral nutrition is provided continuously, 5 units of regular insulin every 6 hours is prescribed. Additional correction insulin is administered as needed. The patient’s average blood glucose is now 160 mg/dL.

**Considerations in Gestational Diabetes**

Multiple placental hormones secreted during pregnancy
medical nutrition therapy

(including estrogen, progesterone, cortisol, placental lactogen, prolactin, and growth hormone) contribute to a state of marked insulin resistance and subsequent carbohydrate intolerance [137]. Even at low levels of glucose intolerance, the risk of perinatal complications from gestational diabetes (eg, macrosomia) is increased [138]. The landmark Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) further established a significant increase in serious adverse perinatal events in participants with gestational diabetes who received routine care versus those who received intensive therapy [139]. Recent evidence also suggests that maternal hyperglycemia has adverse effects on children later in life [140], and women with gestational diabetes are more likely to progress to frank diabetes themselves [141]. As most women with gestational diabetes are treated by diet alone [124], medical nutrition therapy is a critical component of therapy during pregnancy.

Recommended Maternal Weight Gain and Caloric Intake

Multiple studies have shown that women who are overweight or obese prior to pregnancy are more likely to gain excess weight, which later may increase their risk for progression to type 2 diabetes [142]. Additionally, maternal obesity has been shown to be a predictor of the development of metabolic syndrome in children (independent of gestational diabetes) [140]. Although recommendations for weight gain in normal weight (BMI, 19–24.9 kg/m²) and overweight women (BMI, 25–29.9 kg/m²) with gestational diabetes are the same as those that apply to all pregnant women [142], obese women (BMI, > 30 kg/m²) are now advised to limit their weight gain to 11 to 20 lb [142,143].

To control excess weight gain, maintain normoglycemia, and decrease the risk of macrosomia, caloric restriction is recommended for obese women with gestational diabetes [54]. A moderate caloric restriction to 1800 kcal/day (30%–33% reduction of daily caloric intake) is not associated with ketosis or ketonuria. Alternatively, calorie formulas can be used to estimate total needs to further individualize the diet. Snyder and colleagues [144] found, in a retrospective study that examined caloric intake in a group of 353 women with gestational diabetes across all BMI categories, that 30 to 34 kcal/kg (pre gravid weight) for normal-weight women and 23 to 25 kcal/kg (pre gravid weight) for obese women was associated with minimal excess weight gain, euglycemia, and no ketonuria.

Carbohydrate Intake

The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) trial clearly demonstrated that both fasting and postprandial hyperglycemia is associated with adverse effects [145]. As carbohydrates are the main determinant of postprandial glucose levels, several groups have advocated for carbohydrate-restricted and low-glycemic index dietary approaches to gestational diabetes. Since 2002, the ADA has recommended modest carbohydrate restriction (35%–40% of kcal) for gestational diabetes [54]. However, few randomized controlled trials have evaluated the efficacy of low-carbohydrate diets in women with gestational diabetes. Major and colleagues [146] found, in a nonrandomized trial of women with gestational diabetes, that carbohydrate-restriction (< 42% of calories) resulted in significant reductions in postprandial glucose values as compared with the high-carbohydrate group (> 45% of calories from carbohydrate). Fewer women in the low-carbohydrate group required insulin and the incidence of macrosomia was decreased. Although modest carbohydrate restriction may be beneficial, the ADA recommends that a minimum of 175 g of carbohydrates daily be consumed during pregnancy, and that the total carbohydrate content should be distributed evenly throughout the day [54].

Similar to carbohydrate-restricted diets, there is limited evidence to support the use of low-glycemic index diets in women with gestational diabetes. In a recent randomized controlled trial, Moses and colleagues [147] reported that significantly fewer women with gestational diabetes who followed a low GI diet required insulin compared to those who consumed a high GI diet (29% vs. 59%; \( P = 0.023 \)).

SUMMARY

Medical nutrition therapy is an effective adjunct therapy for individuals with diabetes and is associated with decreases in HbA1C of 1% to 2%. Although the ADA recommends that medical nutrition therapy be provided by a registered dietitian, some patients may not have access to a dietitian and it is therefore essential that clinicians and nurses be knowledgeable about medical nutrition therapy. For individuals who are overweight or obese, a modest weight loss of 5% to 10% confers significant benefits in glycemic control and cardiovascular risk factors. No optimal macronutrient distribution has been found to be efficacious for glycemic control. Instead, adherence to a particular diet appears to be the most important factor for success. Reduced energy intake is recommended to promote weight reduction. Weight loss and dietary approaches should be enhanced by the addition of lifestyle modification programs when feasible.

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References


99. Barnard ND, Cohen J, Jenkins DJ. A low-fat vegan diet and a...
134. Korytkowski MT, Salata RJ, Koerbel GL, et al. Insulin therapy and glycemic control in hospitalized patients with diabetes during enteral nutrition therapy: a randomized controlled


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