# The Role of Nutrition in Diabetes Management

## Selected Summaries of a Diabetes Nutrition Roundtable

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## A message from Refaat Hegazi, MD, PhD, Abbott Nutrition, Columbus, OH, USA

In 2010, guest speakers and invited attendees met in Columbus, Ohio, to discuss what proved to be a particularly engaging topic: *The role of nutrition in diabetes management*. As Chairman of this meeting, I am pleased to introduce selected summaries from this roundtable discussion as a way to spread the word about the newest concepts in diabetes nutrition.

Hearing all the latest news about research on nutrition in diabetes is very exciting. Increasingly, studies show that we can actually prevent development of type 2 diabetes through lifestyle factors such as proper nutrition, physical activity and weight management. Many other recent studies show that control of blood glucose in patients who are hospitalized can lower risk for infections, shorten length of stay, and even reduce risk of death.

I invite readers everywhere to take advantage of these reviews of recent research findings, expert opinions, and provoking discussions as a way to stimulate study and conversation among your own colleagues. I hope that this meeting and its selected summaries will ultimately lead the way to helping improve quality of life for the ever-growing population of people with diabetes and at-risk for diabetes around the world.

### Why is diabetes nutrition "hot"?

Here are the numbers, and they are striking. It has been estimated that one in three Americans born in 2000 will develop diabetes in their lifetime; a majority of these cases will be attributed, at least in part, to obesity.[1] Almost one third of US children over 2 years of age are already overweight or obese.[2] There are already 24 million people with diagnosed diabetes, and more than twice that number have prediabetes, with blood glucose levels higher than normal, but not high enough for a diagnosis of diabetes.[3] With diabetes, risks for heart disease and strokes are 2 to 4 times higher than in adults without diabetes.



But nutritional strategies, together with exercise, are acknowledged as effective ways to prevent, delay, or treat diabetes. Some solutions can be found in the form of new nutritional ingredients and supplements, while other strategies involve consumption of usual food in balance and in proper amounts.

### What's next?

It's up to you. I invite you to peruse the selected summaries of *The Role of Nutrition in Diabetes Management*, dig into some of the references cited, and start discussions or hold meetings at your own site. Help fill a knowledge gap by conducting a research study. The possibilities are endless. With your shared interest, we can work together to make a real difference in the lives of millions of people.

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# Diabetes and Glycemic Management

## Glycemic management of subjects with prediabetes

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Obesity, with its inherent risk for diabetes, is a leading public health challenge today. In preparing to advise patients about lowering risk for developing diabetes, physicians benefit from understanding biomarkers of risk and recognizing dietary and lifestyle patterns that are harmful. Excess weight increases risk for diabetes, as does sedentary lifestyle and intake of a usual Western diet.

> To advise patients about lowering risk for developing diabetes, physicians benefit from understanding biomarkers of risk and recognizing dietary and lifestyle patterns that are harmful.

As summarized below, these modifiable risk factors can be addressed to prevent or delay onset of type 2 diabetes.

- **Weight and waist circumference.** For more than a decade, weight change has been associated with incidence of type 2 diabetes. Weight loss ≥5 kg decreases risk by 20%, while weight gain of 5 to 8 kg more than doubles risk, and weight gain >20 kg nearly quadruples risk.[1] Further, large waist circumference serves as a practical and reliable predictor of diabetes—with better predictive value than BMI or other cardiometric risk factors (blood pressure, triglycerides, serum lipoprotein and blood glucose levels).[2] Cutoff points for increased risk are 88 cm (35 inches) for women and 92 cm (36 inches) for men.[3]
- **Physical activity.** Moderate physical activity was supported by a systematic review of 10 studies involving more than 9000 incident cases of diabetes.[4] Taken together, individuals who regularly engaged in physical activity of moderate intensity had ~30% lower risk of type 2 diabetes compared with sedentary individuals.
- **Western diet.** Food groups such as red meat, low-fiber bread and cereal, fried potatoes, eggs, and cheese are prominent in the so-called Western diet, which also commonly includes sweetened beverages, high glycemic index foods, and foods high in saturated fats.[5] Low intake of fresh fruits and vegetables is also common.

There is substantial evidence in the medical literature about using specific strategies to prevent diabetes onset. For example, a review of dietary advice by the Cochrane Group found support in common for reduced intake of energy and simple sugars, along with increased intake of fresh fruits and vegetables.[6] Other protective factors are physical activity, never smoking, moderated alcohol use, BMI <25, and decreasing waist circumference (<88 cm for women, <92 cm for men). Importantly, Mozaffarian and colleagues for the Cardiovascular Health Study determined that combining protective strategies can provide cumulative benefit for diabetes prevention. As expected, increasing the number of low-risk factors yields a greater benefit.[3]

**Table. Recommendations for reduction of diabetes risk[7]**

| Features of intervention | Recommendation |
|---|---|
| **Body weight loss** | ≥5% |
| **Dietary guidelines** | |
| Carbohydrates | ~55% of energy |
| Total fat | <30% of energy |
| Saturated fat | ≤10% of energy |
| Cholesterol | <138 mg/1000 kcal |
| Protein | 10–15% of energy |
| Fiber | 12.5 g/1000 kcal/day |
| **Exercise** | 30 min of moderate physical activity/day, at least 5 days/wk |

Other guidelines are available from sources such as the American Diabetes Association[8] and the Joslin Diabetes Center.[9]

Numerous studies support the benefits of healthy diet, regular exercise, and weight loss when needed to decrease risk for diabetes incidence.[7,10] Roumen and colleagues reviewed studies in order to compile and quantify lifestyle factors associated with diabetes risk reduction (Table). In people with prediabetes (impaired glucose tolerance) the risk of progression to diabetes could be reduced by one half when multiple forms of lifestyle intervention were pooled, as shown by a meta-analysis of 17 studies involving >8000 patients.[10] Many pharmacological interventions helped prevent diabetes, but lifestyle interventions were at least as effective as use of a drug.[10]

### Take-home messages

- Lifestyle modification, including losing 5-10% of initial weight and engaging in 30 minutes of moderately intensive physical activity every day, can provide significant reduction in diabetes risk and should be implemented for all at-risk individuals.
- Dietary components should include recommended amounts of low-glycemic carbohydrates and fiber, and low levels of saturated fat.

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# Nutritional Issues in Subjects with Diabetes

## Is diabetes a nutritional disease?

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The chronic disease of obesity takes many tolls. Its greatest is its association with diabetes incidence,[1] which is increasingly prevalent in the US and around the world.

The link between obesity and diabetes is complex. Scientific evidence suggests a key role for the brain in the control of both body fat content and glucose metabolism.[2] Neuronal systems respond to input from hormonal and nutrient-related signals conveying information regarding both body energy stores and current energy availability. In response to this input, the brain normally regulates energy intake, energy expenditure, and endogenous glucose production to maintain energy homeostasis and blood glucose levels in the normal range. The link between obesity and type 2 diabetes is thought to result from defects in this control system, eg, changes in release of hormones such as leptin and adipsin from adipose tissue.

Since obesity is usually associated with abundant food intake, it may be surprising that people with diabetes experience nutritional deficiencies. However, deficiencies of micronutrients—magnesium, zinc, and chromium—are common.[3] Protein inadequacy is another important shortfall, especially for older people with diabetes. The net result is decline of skeletal muscle function. This condition has recently been recognized as sarcopenia, or sarcopenic obesity when it occurs in people of excess weight.[4]

Sarcopenia is the loss of muscle mass and/or strength, along with a decline in functionality.[5] Such changes are often associated with obesity and insulin resistance, which predispose individuals to development of type 2 diabetes. With sarcopenic obesity, the quality of muscle is further compromised by infiltration of fat. This "marbling" further diminishes muscle function. People with sarcopenia have difficulty walking and climbing stairs and have trouble performing tasks of daily living. They are at increased risk for falls and hip fracture, and even for death. The underlying pathology is thought to be related to deficits in mitochondrial function, especially the function of muscle mitochondria.[6]

A sarcopenia diagnosis should be considered in all older patients who present with observed declines in physical function, strength, or overall health.[5] Sarcopenia can be suspected in patients who are bedridden, cannot rise independently from a chair, or have a measured gait speed <1.0 meter per second. Patients who meet these initial criteria should further undergo body composition assessment using dual energy X-ray absorptiometry. Sarcopenia is defined as lean/fat ratio more than 2 standard deviations below that of an average young adult.

Management of sarcopenia in older people with diabetes depends largely on two strategies: exercise and diet. Since loss of functional abilities has a marked effect on lifestyle and independence of an older person, exercise is important to restore lean body mass.[7] Resistance training has proven highly effective to help older individuals build muscle and improve their ability to perform activities of daily living such as walking, bathing, dressing, and changing from a sitting to a standing position.[7,8]

Protein intake is a key consideration for dietary management of sarcopenia in older people, including the amount and quality of protein and the timing of its intake. While the US Institute of Medicine recommends 0.8 g protein per kg body weight each day for all adults, geriatric clinicians have determined that higher levels of dietary protein may be appropriate for older individuals—up to 1.8 g protein/kg/day.[9] Furthermore, the timing of this protein intake can also be a factor. Paddon-Jones and colleagues recently advised intake of 25-30 g protein at each of 3 meals per day, in contrast to customary intake that is weighted more heavily to protein intake at the evening meal (60 g dinner, 10-20 g at breakfast and lunch).[10]

An important role also has been recognized for intake of leucine, an essential, branched-chain amino acid that acts as a signal to enhance protein synthesis.[11] However, beta-hydroxy-beta-methylbutyrate (HMB), a stable, highly active metabolite of leucine, has recently emerged as a beneficial dietary supplement that stimulates protein synthesis and inhibits breakdown of proteins.[12]


In addition, a role for supplemental testosterone is now being investigated as a way to build and maintain muscle in older people.[8]

Obesity and diabetes are indeed nutritional diseases. Management requires attention to diet, with focus on intake of protein. However, diet alone is not enough. Physical activity, particularly resistance exercise, plays a key role in building and maintaining lean body mass in older individuals with diabetes. Sustained muscle function is vital to continuing with activities of daily living, thereby maintaining quality of life.

### Take-home messages

- Obese people with diabetes often suffer from malnutrition and sarcopenia as they get older, a condition known as sarcopenic obesity.
- Sarcopenic obesity manifests as mitochondrial dysfunction and reduced muscle function.
- Clinical studies of treatment strategies suggest that focus on quantity, quality, and timing of dietary protein may be important to increase muscle mass and strength.
- Nutrition that includes amino acids or metabolites (HMB) is a promising strategy for improved management of sarcopenic obesity. Use of anabolic enhancers also needs further exploration.

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# Nutritional Issues in Subjects with Diabetes

## Protein requirements of subjects with diabetes

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Debate continues about optimal dietary protein intake among people with diabetes. The American Diabetes Association has developed recommendations for medical nutrition therapy (MNT), which include guidance for dietary protein intake.[1] For people with diabetes, a dietary intake of protein representing 15-20% of total energy is recommended (level E, expert recommendation). Body-weight-based intake for protein is suggested as 0.8-1.0 g/kg/day for people with normal kidney function but less for those in later stages of chronic kidney disease (CKD; level B). Selection of MNT that benefits lowering of cardiovascular risk factors is recommended (level C), but a high-protein diet is not recognized as a method for weight loss at this time.

However, clinical study results supported benefits of a high-protein diet (as compared to a high-carbohydrate diet) for obese women who were insulin resistant.[2] The high-protein diet contained 34% carbohydrate and 30% protein, while the high-carbohydrate diet contained 49% carbohydrate and 21% protein. Over the 24-week treatment interval, patients on the high-protein diet showed significantly better BMI-lowering; significant reduction of weight, waist circumference, and triglyceride levels; and more individuals experienced lowering of low-density lipoprotein levels.[2]

### ADA 2008 dietary protein recommendations for people with diabetes[1]:

- Protein as 15-20% of total energy for people with normal renal function (level E)
- With normal kidney function or early-stage CKD, protein as 0.8-1.0 g/kg/day (level B)
- With later-stage CKD, protein as 0.8 g/kg/day (level B)
- MNT that favorably affects cardiovascular risk factors is preferred (level C)
- High protein diet not recommended as a method for weight loss at this time (level E)

### Hamdy's Top 10 Reasons for People with Diabetes and Normal Kidney Function to Increase Protein Intake:

1. Protein does not increase plasma glucose.
2. Protein increases insulin response.
3. Higher protein reduces the need to increase carbohydrates or fat, which can cause other negative effects.
4. Protein reduces appetite and increases satiety.
5. Protein increases thermogenesis.
6. Higher protein enhances weight loss and maintains lean mass.
7. More dietary protein is associated with reduction in total cholesterol, LDL and triglyceride levels.
8. Higher protein intake is associated with reduction in blood pressure.
9. Higher protein intake is associated with reduction in inflammation markers.
10. High-protein diet is linked with fewer cardiovascular events.

Additional studies provided evidence to support benefits of higher-protein diets for people with diabetes, especially those who were obese and insulin resistant. Brinkworth and colleagues found that a high-protein diet (protein as 30% of energy) caused significantly greater weight loss than did a low-protein diet (protein as 15% of energy).[3] Gannon and colleagues found that a high-protein diet caused significantly greater lowering of hemoglobin A1c compared to a low-protein diet.[4] Nevertheless, some clinicians do not recommend high-protein diets for patients with diabetes because of concerns about increasing risks for kidney disease. Does a high-protein diet actually predispose people with diabetes to developing kidney disease? No, a high-protein diet does not raise microalbuminuria, but a diet high in fat does.[5] Further, a high-protein diet improved cardiovascular outcomes in women compared to a diet with lower protein intake.[6]

I recommend the use of moderate protein diets for people with diabetes and prediabetes for weight loss and glycemic management. See page 10 for my top 10 reasons for people with diabetes (and normal kidney function) to increase intake of protein.

### Take-home messages

- For people with type 2 diabetes, increasing protein intake to 1.5-2 g/kg (or 20-30% of total caloric intake) may enhance weight loss, reduce blood pressure, improve lipid profile, and reduce A1c.
- Increasing protein intake to 1.5-2 g/kg/day (or 20-30% of total caloric intake) was not associated with deterioration of renal function in diabetic patients with normal renal function.
- Currently, no data support increasing protein intake above 2 g/kg body weight per day or higher than 30% of total energy intake.

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# Effects of Nutrition on Cardiovascular Disease in Diabetes and Prediabetes

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Nearly 8% of the US population has been diagnosed with diabetes. Double that percentage have prediabetes, or blood glucose levels higher than normal but not high enough for a diagnosis of diabetes.[1] As increasing numbers of people live a sedentary lifestyle and are overweight or obese, the number of new cases of diabetes is growing—at least 1.6 million new cases are diagnosed each year. The price tag for these new cases is reflected in dollars (the direct cost of health care for people with diabetes has been estimated at $116 billion per year[2]) and in co-morbidities: diabetes is the leading cause of end-stage renal disease and the most common cause of blindness in working-aged adults; the most prominent cause of lower-extremity amputations for non-traumatic cause; and is associated with a 2- to 4-fold increase in risk for cardiovascular disease.[1]

Dyslipidemia and hypertension are risk factors common to cardiovascular disease and to diabetes. In combination with hyperglycemia, these modifiable risk factors are targeted for management of diabetes. Target levels for diabetes control are hemoglobin A1c level lower than 7.0%; blood pressure less than 130/80 mm Hg; and low-density lipoprotein (LDL) cholesterol below 100 mg/dL.[1] A recent US report found that only 12% of Americans with diabetes have been able to meet all three of these targets.[3]

> To lower risk for heart disease, therapeutic lifestyle changes (TLC) are recommended—increased physical activity, weight reduction, and a TLC diet.

Therapeutic lifestyle changes (TLC) are advised to lower risks for heart disease. Changes include increased physical activity, weight reduction, and a TLC diet (Table).[4] Recommendations limit intake of fat to 25-35% of total energy, with emphasis on inclusion of healthier monounsaturated fatty acids (MUFA) over saturated and polyunsaturated fats. The TLC diet also recommends an intake that is high in fiber and includes moderate amounts of protein and low amounts of cholesterol. Importantly, this diet recommends balancing caloric intake with energy output in physical activities in order to prevent weight gain.

**Table. Nutrient composition of TLC diet**

| Dietary component | Recommended intake |
|---|---|
| Saturated fat | <7% of total calories |
| Polyunsaturated fat | Up to 10% of total calories |
| Monounsaturated fat | Up to 20% of total calories |
| Total fat | 25-35% of calories |
| Carbohydrate | 50-60% of calories |
| Fiber | 20-30 g/day |
| Protein | ~15% of total calories |
| Cholesterol | <200 mg/day |
| Total calories | Balance intake and output to prevent weight gain |

Evidence supports the inclusion of some specific dietary components for heart health—plant stanols, soluble fiber, omega-3 fatty acids (such as fish oil), and MUFA (as in canola and olive oil) while minimizing intake of trans fatty acids and otherwise limiting consumption of polyunsaturated fatty acids (PUFA). Clinical studies support consumption of MUFA to help maintain low LDL and triglyceride levels, while increasing high-density lipoprotein (HDL) levels.[5] Diets high in marine oils (rich in eicosapentaenoic acid, or EPA) have been shown to protect against incidence of coronary artery disease and major coronary events.[6,7]

For heart benefits, low-glycemic carbohydrates are recommended in the form of whole grains, vegetables and fruit, with dietary fiber totaling more than 25 g/day.[5,8] Soluble fibers (eg, oat products, beans, psyllium, guar gum, soy products, pectin) are recognized to lower LDL levels. When taken at a dose of 2 g/day, plant sterol and stanol esters are effective in lowering LDL cholesterol by 6-15%.[5] Dietary recommendations such as these have allowed my patients to reduce their risk factors for cardiovascular disease.

## Take-home messages

- In the US, diabetes is a common and costly disease that takes a high toll on cardiovascular health.
- Therapeutic lifestyle changes (healthy low-fat diet, exercise, and weight reduction) are recommended to lessen risk for cardiovascular disease.
- Specific heart-healthy dietary nutrients include soluble fiber, omega-3 fatty acids, and plant stanols/sterols.

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# Management of Tube Feeding-associated Hyperglycemia

## Medical management

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Hyperglycemia is a common side effect for patients receiving enteral feeding.[1] Hyperglycemia requires aggressive, coordinated treatment in the hospital setting. This treatment should begin at admission with the patient history, as well as an assessment of blood glucose level and glycated hemoglobin (hemoglobin A1c). These data allow caregivers to establish appropriate delivery methods and levels of glucose control during the hospitalization and to develop dismissal plans with recommendations for follow-up testing and care.

> Hyperglycemia is a common side effect of patients with enteral feeding. Managing hyperglycemia starts at admission and ends with appropriate dismissal plans for follow-up testing and care.

For enteral nutrition patients with stable type II diabetes and normal renal and kidney function, oral diabetic agents may be provided via the feeding tube; however, metformin should not be used in the hospital. Patients treated with insulin prior to admission or with blood glucose levels consistently >150 mg/dL need insulin, and may be broken into three categories[2]:

- Most patients require 0.5-0.7 units of insulin/kg/day.
- Patients with type I diabetes, lean body weight, renal dysfunction, hepatic dysfunction, or an age greater than 65 years usually require a lower total daily dose of insulin (ie, 0.3-0.5 units/kg/day).
- Patients with type II diabetes, a BMI >30, post-myocardial infarction, an infection, or are receiving corticosteroids usually require a higher total daily dose of insulin (ie, 0.5-1.5 units/kg/day).

Patients who are receiving combination insulin preparations (mixtures of intermediate and rapid or short-acting insulin) on admission need to be converted to basal/bolus therapy where a long-acting basal insulin is supplemented with a rapid or short-acting insulin for meals or blood glucose level correction during hospitalization (Table). The provision of only sliding scale insulin (SSI) is a reactive rather than proactive response to hyperglycemia; SSI has been shown in non-critically ill patients to be three times more likely to cause hyperglycemic events.

In addition to the above criteria, blood glucose management in enteral nutrition patients requires adaptation under the following special conditions:

- If feeding is infused during the day, initially administer ½ of the preadmission morning insulin dose as an intermediate-acting insulin.
- Twice daily intermediate-acting insulin (eg, NPH) is often needed if feeding is continuous.
- If feeding is infused overnight, intermediate-acting insulin should be administered in the evening.
- Short-acting insulin should be added if glucose goals are not achieved.
- For gravity administration, check glucose levels prior to feedings and no sooner than 4 hours after end of prior feeding.
- The feeding rate should not be advanced until glucose control is adequate. If the feeding rate is increased, the dose of intermediate-acting insulin should be increased.
- In patients with unsatisfactory glucose control or unstable course, an intravenous insulin infusion should be started.

Finally, the establishment of blood glucose level goals is crucial to the management of hyperglycemia for hospital patients receiving enteral nutrition. These goals will vary according to the status of the patient[3]:

- For critically ill patients (those in Intensive Care) a blood glucose level of 100-120 mg/dL.
- For non-critically ill patients a blood glucose level of 120-180 mg/dL.

**Table. Selected insulin preparations with their onset, peak and duration[2]**

| Rapid & Short-acting Insulins | Onset | Peak | Duration |
|---|---|---|---|
| Lispro | 5-15 minutes | 1-2 hours | 4-6 hours |
| Aspart | 5-15 minutes | 1-2 hours | 4-6 hours |
| Glulisine | 5-15 minutes | 1-2 hours | 4-6 hours |
| Regular | 30-60 minutes | 2-4 hours | 6-10 hours |

| Intermediate & Long-acting Insulins | Onset | Peak | Duration |
|---|---|---|---|
| NPH | 2-4 hours | 6-12 hours | 12-18 hours |
| Glargine | 2-4 hours | None | 24 hours |
| Detemir | 2-4 hours | None | 24 hours |

### Take-home messages

- Effective management of tube feeding-associated hyperglycemia involves aggressive treatment even for those patients without a known history of diabetes. The establishment of blood glucose level goals is primary.
- Insulin is the preferred treatment because of its easy titration and rapid achievement of glycemic control. Basal/bolus therapy—long-acting basal insulin combined with short-acting bolus insulin— should be used during hospitalization.
- For enteral nutrition patients, establishing blood glucose level goals is critical for managing hyperglycemia. Blood glucose management also may require adaptation under some special conditions.

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# Management of Tube Feeding-associated Hyperglycemia

## Nutritional management of enteral nutrition-associated hyperglycemia

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Hyperglycemia is common in hospital settings. In a study of patients admitted to a US community hospital, about 1 of every 3 patients had hyperglycemia.[1] Numerous guidelines and standards set goals for clinical management of diabetes in outpatients, but evidence-based standards of care for inpatients have only recently become available. Hospitalized patients can experience hyperglycemia due to underlying diabetes or to the metabolic stresses of illness.[2,3]

Hospitalized patients with poorly controlled glucose levels face serious consequences, including increased risk of infections, impairment of wound healing, gastroparesis, hypercatabolism and muscle wasting, increased length of ICU or hospital stay, and increased mortality rates. Regardless of the cause of hyperglycemia, studies in hospitalized patients have shown improved outcomes when the hyperglycemia is treated.[4]

In hospitalized patients, adverse consequences of poor glucose control include:

- Increased risk of infections
- Impairment of wound healing
- Gastroparesis
- Hypercatabolism and muscle wasting
- Increased length of ICU or hospital stay
- Increased mortality rates

The Society of Critical Care Medicine (SCCM) and the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) recently updated nutrition guidelines for critically ill patients.[5] With regard to control of glycemic status, the guidelines recommend:

- Use protocols to promote moderately strict glycemic control in patients receiving enteral nutrition-support therapy. (Grade B)
- Target serum glucose in the range of 110-150 mg/dL. (Grade E)

Nutrition-support dietitians play important roles in the care of hospitalized patients with poor glucose control.[6] To achieve best results, dietitians need to (1) know what factors affect glycemic control and the rationale for minimizing glycemic variability, (2) understand current recommendations for gaining optimal glycemic control, and (3) implement nutrition therapy that will safely achieve and maintain glycemic control without inducing hyper- or hypoglycemia.

When enteral nutrition (EN) is prescribed, the first consideration is the access point—should the patient be tube-fed via the stomach or jejunum? What strategies can be employed to achieve and maintain glucose control? Is continuous or intermittent EN infusion preferred? Should the patient receive a standard formula, a high-fiber formula, or a diabetes-specific formula?

With tube-fed EN, the overall goal is to prevent hyperglycemia and hypertriglyceridemia, which are associated with negative outcomes. It is thus important to avoid carbohydrate overfeeding that can drive *de novo* fat synthesis in the liver. In hospitalized patients, insulin treatment is often preferred over anti-diabetic agents. To avert hypoglycemia when EN is interrupted during intensive insulin therapy, our procedure advises hanging 5% dextrose in water (D5W) at 1.5 times the hourly tube-feeding rate or 10% dextrose in water (D10W) at the tube-feeding rate.

To moderate risk for glucose variability, a large body of research supports the use of diabetes-specific enteral nutrition.[7-9] Such formulas contain slowly absorbed carbohydrates and healthy monounsaturated fats as energy sources that help blunt postprandial rises in blood glucose.

There are sound, evidence-based justifications for control of blood glucose levels in hospitalized patients, with better control yielding better outcomes. Especially when intensive insulin therapy is used for control, it is important to avert episodes of hypoglycemia. Nutrition can play an important role in helping limit glucose variability. Diabetes-specific nutritional formulas are well-supported as part of safe and effective glucose management in hospitalized patients.

### Take-home messages

- Management of EN-associated hyperglycemia in hospitalized patients can be challenging.
- There is compelling evidence for benefits of minimizing glycemic variability in all EN-fed patients.
- To achieve the optimal nutrition status for each patient, the nutrition-support clinician needs to consider the route, timing, quantity, and composition of the feeding.
- A large body of research supports the use of diabetes-specific EN formulas in the management of hospitalized patients.

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# Diabetes-specific Formulas: Science and Technology

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For people with diabetes, medical nutrition therapy is an important component of glycemic control—along with medical management of the disease and regular monitoring of glycemic status. Management of glycemia in the hospital setting is particularly important because hyperglycemia is associated with increased morbidity and mortality in patients with and without diabetes.[1] Specifically, hyperglycemia impairs immune function, delays wound healing, increases susceptibility to infection, and increases length of hospital stay.

Diabetes-specific nutrition formulas are designed to provide quality nutrition and they include features to help improve glucose control.[2] Examples of such features are: (1) carbohydrates that are modified to be digested and absorbed slowly (based on unique glucose-glucose or glucose-fructose linkages), (2) inclusion of healthy monounsaturated fats to help lower plasma triglycerides and increase HDL cholesterol levels,[3] and (3) high fiber content for gut health and glucose control. For people with hyperglycemia, diabetes-specific nutrition can reduce the need for additional insulin to maintain glycemic control, while standard formulas often necessitate more time and medications to control blood glucose.[2]

Here are the key studies that underscore benefits to using diabetes-specific nutrition.

**Elia and colleagues**[2] reviewed and conducted a meta analysis on 23 studies comparing diabetes-specific nutrition with standard nutrition. They found that the use of diabetes-specific formulas significantly lowered postprandial blood glucose, peak glucose, and area under the curve for glucose. These improvements were demonstrated with short- and long-term use. Long-term use may have implications for reducing chronic complications of diabetes. Additionally, several studies showed significant reduction in insulin requirements (26% to 71%).

**Voss et al**[4] conducted a clinical research study to compare diabetes-specific nutrition formulas and a standard nutrition formula. Participants who fasted overnight consumed a serving of formula, and were then monitored for effects on blood glucose, insulin, and glucagon-like peptide-1 (GLP-1) responses. Results showed significantly lower post-meal glucose and insulin levels with diabetes-specific nutrition, and significantly higher levels of GLP-1.

**The LOOK Ahead Study**[5] was designed to determine the effectiveness of intentional weight loss for reducing cardiovascular events in people with type 2 diabetes. More than 5000 people participated in this study, and the intervention included: (1) portion-controlled diet that includes liquid meal replacement, (2) multi-component approach to intervention, (3) ongoing regular contact with participants throughout the follow-up period, and (4) weight-loss medications and advanced behavioral strategies in later months of study, as needed. After just 1 year, beneficial results were already apparent—with decreases in body weight and lowered A1c levels, fasting glucose levels, and triglyceride levels in intensive-lifestyle-managed patients compared to standard-care patients.

A study by **Sun and colleagues**[6] used a structured integration management program to assess diabetes control in overweight people with type 2 diabetes. The study included 150 patients with type 2 diabetes who were randomized to either the treatment group or control group. Patients in both groups received dietary and exercise counseling and diabetes education. The patients in the treatment group also replaced part of their breakfast with the diabetes-specific product. By the end of the 6-month study, haemoglobin A1c levels were significantly reduced in the intervention group on diabetes-specific nutrition compared to the control group.

**Alish and colleagues**[7] conducted a study to compare the 24-hour glucose responses in patients with type 2 diabetes who were tube-fed a standard formula versus a diabetes-specific formula as sole-source nutrition for 16 h/day over 4 days. Glycemic variability, measured with a continuous glucose monitor and expressed as mean amplitude of glucose excursions, was significantly lower with feeding of diabetes-specific nutrition. There was also a 28.4% reduction in the amount of short-acting insulin needed to manage blood glucose levels.

| Diabetes-specific nutrition formulas | Standard nutrition formulas |
|---|---|
| Modified carbohydrate is digested and absorbed slowly, a benefit to people with poor glucose control | Rapidly digested carbohydrate predisposes to high postprandial glucose rise in people with poor glucose control |
| Healthy monounsaturated fats used | Low in fat |
| High in fiber | Low in fiber |
| Enable better glycemic control, including control of postprandial rise | May compromise glycemic control |

## Take-home messages

In clinical studies, diabetes-specific nutrition formulas have been shown to:

- Improve post-meal responses, as measured by lowered glucose and insulin and increased GLP-1 responses.
- Improve weight management, as in the LOOK Ahead study of people with type 2 diabetes.
- Improve hemoglobin A1c levels when used as part of an integrated diabetes intervention program.
- Lessen glycemic variability and reduce the amount of short-acting insulin needed to manage blood glucose levels in tube-fed patients with diabetes.

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# Diabetes-specific Nutrition in the Outpatient Setting

## Diabetes-specific nutrition in subjects with diabetes mellitus

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The importance of diet has long been recognized as a key element in diabetes management. Specific goals of dietary management are to promote glycemic control (in concert with medications and exercise), to improve the lipoprotein profile and prevent vascular disease complications, and to facilitate weight loss in those who are overweight or obese. As new strategies emerge for diabetes management, the dietary component of treatment remains the mainstay for full effectiveness.

### Goals of dietary management for diabetes:

- To promote glycemic control (in concert with medications and exercise)
- To improve lipoprotein profile and prevent vascular disease complications
- To facilitate weight loss in those who are overweight or obese

This presentation provided an overview of what the future of diabetes therapy may look like.

**Diabetes Prevention.** It is no longer sufficient to wait until diabetes is overt to begin treatment. There is now a national mandate for diabetes prevention. The mandate calls for combined recommendation of diet and increased physical activity as lifestyle interventions to promote weight loss and lower risk for cardiometabolic disease.[1,2] This approach recognizes obesity, insulin resistance, metabolic syndrome, and prediabetes (impaired fasting glucose, impaired glucose tolerance) as conditions along the continuous spectrum toward full-blown diabetes. As such, recognition and management of the precursor conditions are essential to prevent or delay the onset of diabetes. Diets rich in fresh fruits and vegetables along with calorie-controlled meal replacements are useful in this strategy—along with increased exercise.

**New Obesity Medications.** A wide range of obesity medications are now in phases 2 or 3 of testing or undergoing review by the US Food and Drug Administration. These include serotonin agonists (eg, lorcaserin); multiple amine reuptake inhibitors (eg, tesofensine); glucagon-like peptide-1 agonists (eg, liraglutide); combined phentermine + topiramate (eg, Qnexa®); combined bupropion + naltrexone (eg, Contrave®); and combined amylin + leptin (eg, metreleptin + pramlintide). Despite the promising effects of these drugs, all will need to be used together with diet and exercise.

**Bariatric Surgery.** At the present time, bariatric surgery is significantly and conclusively more effective at producing sustainable weight loss and controlling comorbidities than available medical treatments.[3,4] However, dietary strategies are still needed to enhance outcomes for bariatric surgery, including pre- and postoperative weight loss, as well as postoperative nutrition. Dietary strategies are also important to reverse micronutrient deficiencies that can result from the gastrointestinal alterations of surgery.

**The Incretin Axis.** Incretins physiologically regulate glucose by modulating insulin secretion in a glucose-dependent manner. Incretins include GIP, GLP-1, and DPP-4 inhibitor.[5,6] Dietary intervention, ie, meal replacement beverages, have been shown to act synergistically with incretin axis drugs.[7]
There are many new options that offer promise for better control of weight and lowering of risk for diabetes and cardiovascular disease. The role of diet (including meal replacement) is foremost. Active lifestyle, obesity medications, incretin-axis drugs, and bariatric surgery can be integrated into the management program as needed.

### Take-home messages

Use dietary strategies in combination with other approaches for management of weight and diabetes.

- Diet, including use of meal replacements, is a key component of a comprehensive weight loss program for prevention and treatment of diabetes.
- Diet is an important adjunct to new weight loss medications. In the future, there will likely be new uses for incretin-axis drugs as strategies for management of body weight and lowering risk for diabetes.
- Before and after bariatric surgery, an appropriate diet helps to achieve weight loss, maintain healthy body weight, and reverse micronutrient deficiencies.
- An integration of multiple strategies, with diet playing a key role, will be important to facilitate weight loss and manage diabetes.

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# Diabetes-specific Nutrition in the Outpatient Setting

## Diabetes-specific nutrition for subjects with co-morbidities

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Diabetes is a chronic, multisystem disease that requires attention to co-morbidities for optimal management.[1] Many of the co-morbidities of diabetes are common to the overlapping conditions of insulin resistance and obesity. These include renal disease, cardiovascular disease, neuropathy, gastroparesis, myopathy, dyslipidemia, and inflammation.

Co-morbidities associated with diabetes, insulin resistance, and obesity:

- Renal disease
- Cardiovascular disease
- Neuropathy
- Gastroparesis
- Myopathy: skeletal and heart
- Inflammation

Dietary strategies are prominently used to address these co-morbidities. The following summary describes how diet can be tailored to address problems characteristic of various co-morbidities:

**Renal Disease.** Kidney disease is a common complication of diabetes, and this condition increases risk for *protein-energy wasting (PEW).*[2] Kidney disease-associated PEW is rooted in abnormal energy metabolism that is associated with changes in central and peripheral control signals. Such changes impair nutrient intake and utilization by way of many contributing factors—inflammation, catabolism, oxidative stress, uremia, anorexia, nutrient loss by dialysis or medication effects, and physical inactivity. The end result of PEW is loss of physical function, lower quality of life, and higher risk of death. Specialized nutrition, including high energy with or without high protein, is necessary to help overcome nutritional deficits in patients with chronic kidney disease. In early stages of disease, it is necessary to limit protein intake to help slow decline of kidney function in pre-dialysis patients. Once dialysis begins, protein intake can be increased to compensate for losses.

**Cardiovascular Disease.** Medical treatment is used commonly to help correct altered lipid states that increase risk for cardiovascular disease (elevated triglycerides and low-density lipoproteins, lowered high-density lipoproteins), but diet is also important. The American Heart Association recommends limiting dietary saturated fat intake to <7% of total calories, trans fats to <1% of calories, and cholesterol to <300 mg/day.[3] Likewise, consumption of fish (rich in omega-3 eicosapentaenoic acid, EPA; docohexaenoic acid, DHA) is recommended to lower cardiovascular risk.[3]

**Neuropathy.** Glycemic variability (GV) is defined as the variations in glucose levels from peak to valley. It has recently been acknowledged that GV may be more deleterious than constant exposure to high glucose, especially due to escalated likelihood of increasing oxidative stress, which can damage the endothelial tissues.[4] It is thought that kidney damage and other complications can be lessened by using dietary strategies that stabilize glycemic variability.

**Myopathy.** Muscle myopathy or weakening can affect both skeletal and cardiac muscles. One way to limit these effects is to balance dietary provisions of glycolytic and oxidative (non-ketotic) fuels.

**Inflammation.** Inflammation (associated with inflammatory cytokines and other mediators) is associated with obesity and recognized as a possible cause of its morbidities.[5] Dietary advice to reduce inflammation includes increasing intake of omega-3 fatty acids such as EPA and employing dietary strategies that will reduce visceral adiposity.

### Take-home messages

Dietary changes are strategic to lowering risk for co-morbidities of diabetes, insulin resistance, and obesity.

- In patients with chronic kidney disease, specialized nutrition, including high energy with or without high protein, is necessary to help overcome nutritional deficits. Dietary protein is determined by the capacity of the kidneys.
- Risk of cardiovascular disease can be reduced by limiting intake of saturated fat to <7% of total calories, trans fats to <1% of calories, and cholesterol to <300 mg/day.
- Complications can be averted or lessened by using dietary strategies to stabilize glycemic variability.
- Dietary advice to reduce inflammation includes increasing intake of omega-3 fatty acids such as EPA and employing dietary strategies that will reduce visceral adiposity.

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# Diabetes-specific Nutrition in the Inpatient Setting

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Numerous studies have shown that hyperglycemia is common among hospitalized patients—not only in those with diabetes but also in those without. In fact, hyperglycemia is present in 50–85% of critically ill patients. Of these, about 25% have diabetes and others are experiencing stress hyperglycemia.[1] In patients with critical illnesses, hyperglycemia is associated with significantly increased risk for infections and death.[2,3] The converse is also true: improved glycemic control can lead to improved outcomes.

> In patients with critical illnesses, hyperglycemia is associated with significantly increased risk for infections and death.

The most influential interventional study of glucose management was that of Van den Berghe published in 2001—a study of surgical ICU patients in a single center (the Leuven-I study from Belgium). This randomized, controlled study compared intensive insulin therapy (blood glucose levels at 80-110 mg/dL) with conventional treatment (maintenance goal of 180-200 mg/dL). Leuven-I results showed that intensive treatment led to a significant and dramatic 34% reduction in mortality, and the authors concluded that aggressive insulin treatment could improve survival in a variety of critically ill patients.[4] The results were so dramatic that adoption was widespread.

However, a subsequent study by Van den Berghe and colleagues (Leuven-II) did not confirm the mortality benefit of intensive insulin therapy for patients in the medical ICU.[5] In fact, rates of hypoglycemia were significantly greater in patients on intensive insulin therapy compared to conventional treatment (18.7% vs 3.1%). As tight glucose control practices became more widespread, accumulating medical evidence began to show that such management had attendant risks for increased hypoglycemia, which can itself be life-threatening.[6-8]

My colleagues and I recently published results of a study on restriction of carbohydrate as a way to manage glycemia in critically ill patients.[9] In this study, patients (n=337) were randomized to receive carbohydrate-restrictive enteral formula (33.3% carbohydrate, 16.7% protein and 50.0% lipid; also called diabetes-specific nutrition), glucose-free hydration, and insulin therapy with moderate glycemic targets (below 180 mg/dL; <150 mg/dL in stable patients) or to a standard diet (45% carbohydrate, 17% protein, and 38% lipid), glucose-saline hydration, and intensive insulin therapy with tight-control glucose targets (below 180 mg/dL; 80-120 mg/dL in stable patients). Results showed that patients on the carbohydrate-restrictive diet required significantly less insulin each day (mean 2 U regular insulin vs 52 U; $P < 0.001$). Mean blood glucose was 144 mg/dL in the carbohydrate-restrictive group and 133.6 mg/dL in the control group. Hypoglycemia occurred significantly more frequently in the control group than in the carbohydrate-restrictive group (16% vs 3.5%, $P < 0.001$) and was an independent risk factor for neurological dysfunction and mortality.

> Carbohydrate-restrictive enteral nutrition is as effective as intensive insulin therapy for managing glycemia in critically ill patients, and it is safer.

Thus, carbohydrate-restrictive therapy is safer and is as effective as intensive insulin therapy for managing glycemia in critically ill patients. Our study extended these findings to show that there was no difference in incidence of acute kidney injury in patients who received carbohydrate-restrictive nutrition compared to intensive insulin therapy.[10]

I advise the following to achieve target blood glucose levels in critically ill patients: (1) minimize use of intravenous fluids that contain glucose, (2) administer insulin only when necessary, (3) introduce enteral nutrition early, and use a formula that is low in carbohydrate.



## Take-home messages

- In hospitalized patients with critical illness, hyperglycemia is associated with increased risk for infections and mortality.
- Leuven-I study results indicated that aggressive insulin treatment could improve survival in surgical ICU patients. Subsequent studies showed that intensive insulin therapy had attendant risks for increased hypoglycemia, which can itself be life-threatening.
- New studies by de Azevedo and colleagues showed that diabetes-specific nutrition therapy is as effective as intensive insulin therapy for managing glycemia in critically ill patients, and it is safer.

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# Diabetes-specific Nutrition in Subjects with Stress Hyperglycemia

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Hyperglycemia is an independent marker for in-hospital mortality.[1] It can result from underlying diabetes or from the metabolic stress of illness[2,3] and is associated with increased complications and increased length of stay (ICU and hospital).

The adverse consequences of stress hyperglycemia may be even worse than those associated with diabetic hyperglycemia—glucose levels of stressed patients can be highly elevated and have extreme fluctuations from peak to nadir. Like hyperglycemia, severe hypoglycemia is also a marker of poor outcomes. In the ICU, hypoglycemia has been linked to increased mortality, seizures, and coma.[4,5]

> The adverse consequences of stress hyperglycemia may be even worse than those associated with diabetic hyperglycemia.

Diabetes-specific nutrition (DSN) is an effective strategy to control hyperglycemia without risk for hypoglycemia in hospitalized patients. A DSN formula has been designed with digestion-resistant starch and high content of monounsaturated fatty acids (MUFA). In clinical testing, this formulation blunted the post-meal glucose response and reduced insulin requirements in patients with diabetes.[6] Patients who received this DSN also showed evidence of increased production of the incretin hormone glucagon-like peptide-1 (GLP-1).[6] GLP-1 is released from the digestive tract, in turn increasing pancreatic secretion of insulin in response to glucose or a carbohydrate-containing meal. Such a mechanism is thought to represent forward-regulation of insulin in anticipation of the rise in blood glucose that normally follows ingestion of carbohydrates.

Recently, a new concept called glycemic variability has been introduced. Glycemic variability may be an even more important predictor of mortality in the critically ill patient than the mean glucose level. High variability of blood glucose levels can result in increased mortality and permanent neurological disabilities. As a result, glycemic variability has become an important target for in-hospital regulation. Glycemic variability, which is measured by continuous glucose monitoring technology, can be used to measure Mean Amplitude of Glycemic Excursions (MAGE), where amplitude is the difference between peak and nadir values. A recent study used MAGE to compare effects of DSN and standard enteral formula fed continuously for 5 days (16 h/day) in hospitalized patients.[7] Results showed that DSN feeding significantly reduced glycemic variability (MAGE), postprandial glycemia and insulinemia, mean glucose levels, and insulin use.

We recently extended the observation of improved glucose control with DSN in a study of patients with stress hyperglycemia.[8] We compared use of a DSN formula with digestion-resistant starch to a DSN formula without this feature. Both formulas lowered mean glucose levels in the study patients, but the formula with digestion-resistant starch was more effective.

These findings show that diabetes-specific nutrition can be used to help maintain glucose homeostasis in hospitalized patients with or without diabetes. DSN effectively blunts post-meal glucose and insulin rises, increases post-meal GLP-1 levels, and reduces glycemic variability. Such effects are expected to reduce risks for in-hospital morbidities and mortality.

## Take-home messages

- Non-diabetic patients with critical illness can experience hyperglycemia due to the metabolic stresses of illness.
- The consequences of stress hyperglycemia may be even worse than those of diabetes-associated hyperglycemia.
- Feeding a diabetes-specific enteral formula with slowly digested carbohydrate can reduce average blood glucose level and insulin requirements in patients with stress hyperglycemia.
- Diabetes-specific nutrition also increases production of glucagon-like peptide-1 (GLP-1). GLP-1 is an incretin hormone that modulates glucose homeostasis. Its regulation may be a key to improving glucose homeostasis.
- A diabetes-specific enteral formula has also been shown to reduce glycemic variability in hospitalized patients.
- Diabetes-specific nutrition formulas are not all equally effective.

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# A closing message from Refaat Hegazi, MD, PhD

Dear Colleagues,
As our conference on *The Role of Nutrition in Diabetes Management* comes to an end, I feel a mix of emotions.

I am delighted that we could gather such an outstanding panel of experts from the fields of nutrition, endocrinology, pharmacy, gastroenterology, intensive care medicine, and basic science for lively, informed discussions. I am excited that we had an opportunity to hear state-of-the-art summaries from renowned speakers in the fields of obesity, diabetes, exercise, and nutrition. And I am pleased we could host this congenial meeting in the comfortable setting provided by Abbott Nutrition in Columbus, Ohio.

But I am also concerned. Our discussions raised many questions about information gaps that need to be filled. We have much work ahead of us in our efforts to achieve near-normal glycemic control for people both in and out of the hospital. We must galvanize our efforts to use nutrition as a means to help reverse hyperglycemia, reverse hypoglycemia, and limit glycemic variability. We must combine our fresh knowledge of nutrition to help prevent or delay the onset of diabetes. And we must work together to use our new insights to achieve optimal glucose control in order to lessen short-term consequences and long-term tolls of glucose abnormalities.

Now that this roundtable discussion is done, we must engage our clinical and scientific colleagues around the world. Together we are challenged to turn our knowledge into actions that will improve the health and well-being of millions of people with or at-risk-for diabetes. Following this message is a summary of key issues and questions that surfaced during this meeting.

Refaat Hegazi, MD, PhD
Medical Director, Abbott Nutrition



# Nutrition and Diabetes: Challenges for the Near Future

## Glycemic management in people with prediabetes and diabetes

- How can we motivate all people to combine nutrition and exercise to prevent or delay the onset of diabetes?
- What are the optimal glycemic targets for people with diabetes in and out of the hospital? Should they be the same or different, and why?

## Nutritional considerations for people with diabetes

- What is the role of nutrition in averting or diminishing adverse consequences of diabetes on cardiovascular function?
- How do certain dietary ingredients, eg, fish oil and antioxidant vitamins, play functional roles in health?
- How and why do protein requirements differ in people with diabetes compared to those without diabetes?

## Stress hyperglycemia in hospitalized patients

- What are the safest and most effective medical strategies to manage stress hyperglycemia?
- How can nutrition be employed as a tool for managing stress hyperglycemia?

## Science and technology in diabetes-specific nutritional formulations

- How are modified carbohydrates used to limit postprandial glucose rises in people with diabetes?
- What is the most beneficial fat blend to limit cardiovascular complications of diabetes?
- What are the benefits of micronutrient repletion?
- What amounts and types of fiber are optimal for the diet of a person with diabetes?

## Use of diabetes-specific medical nutrition for people in and out of the hospital

- For people with diabetes living at home, how can diabetes-specific nutrition be optimized to improve weight loss and glycemic status?
- What are the roles for diabetes-specific nutrition in hospitalized patients with diabetes?
- What are the roles for diabetes-specific nutritional formulations for hospitalized patients who have stress hyperglycemia?

# The Role of Nutrition in Diabetes Management

Selected Summaries of a Diabetes Nutrition Roundtable
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