

Case Study: Five Steps to Freedom: Dose Titration for Type 2 Diabetes Using Basal-Prandial-Correction Insulin Therapy

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Presentation of a Hypothetical Patient

Mary, age 53, was seen as a new patient. She had a history of type 2 diabetes for 17 years. Her BMI was 31 kg/m². She had attempted to adhere to lifestyle measures for treatment of diabetes and had previously consulted with diabetes educators. She was fairly active at her job.

She was taking 90 units of peakless insulin (glargine) at bedtime in addition to pioglitazone, 45 mg daily; metformin, 1,000 mg twice daily; and glimepiride, 8 mg daily. Her hemoglobin A_{1c} (A1C) was 8.5%. She had average prebreakfast glucose readings of 110 mg/dl. At other times of day, there were premeal glucose readings of 170–240 mg/dl and some peak postprandial readings > 300 mg/dl.

Under the supervision of her previous health care provider, over a 12-month period of combined glargine and triple oral therapy, the strategies of changing the time of peakless insulin administration to the morning and, later, splitting the peakless insulin dose into equal morning and bedtime components had failed to change her blood glucose pattern. A conceptual diagram of the average daily excursions of blood glucose at the time of her presentation is shown in Figure 1.

At the conclusion of the visit, she commented that she wanted to do whatever was necessary to get better results, and she agreed to replace the glimepiride with prandial use of insulin. The glimepiride was discontinued. The pioglitazone dose was reduced to 30 mg daily, with consideration of possible future discontinuation because of cost factors. The metformin was continued.

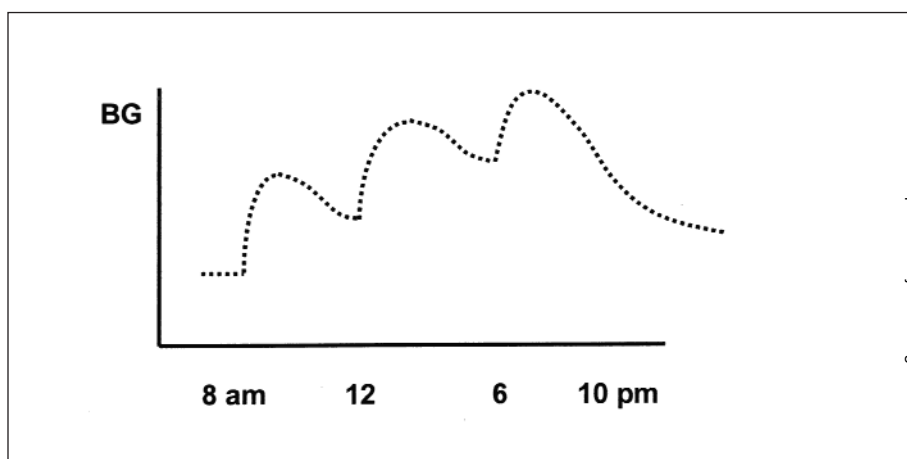


Figure 1. Pattern of blood glucose suggesting insufficient prandial insulin effect.

The combined total amount of the starting doses of insulin under a basal-prandial-correction regimen was assigned at 80% of the former peakless insulin dose. The insulin was divided into 36 units of peakless insulin at bedtime and 12 units of prandial insulin at each of the three major meals.

Recognition of single 15-g servings of carbohydrate was reinforced. As a temporary plan, a consistent carbohydrate diet including 60 g of carbohydrate at the major meals was recommended to the patient. She was issued with an insulin dose titration schedule, with change dates entered by the practitioner, such that an upward dose adjustment would be made every third day, alternating between a 2-unit increment of each of the three premeal lispro doses or a 6-unit increment of the bedtime glargine dose. The one-page handout given to the patient is shown in Figure 2.

Mary was instructed to revisit within 4 weeks or, if some readings approached target, to phone or visit sooner for pat-

tern review. At that point, she was to discontinue the forced titration of insulin.

As Mary's blood glucose readings approached target, in order to achieve pattern adjustment, the practitioner adjusted specific components of the insulin therapy. The doses were revised as follows: 20 units of rapid-acting insulin analog at meals and 60 units of peakless insulin at bedtime. The patient revisited the diabetes educator with her logbook showing 1 week of recorded mealtime intake (still ~ 60 g or four servings of carbohydrate at each meal); unusually heavy activity on two days accompanied by symptomatic lows; blood glucose readings; and insulin doses taken.

An insulin-to-carbohydrate ratio was identified (5 units per serving), and, in terms appropriate to her educational level, the patient received education on how to use the ratio. A simple correction rule was described for taking extra amounts of rapid-acting analog before meals if her blood glucose was high: for blood glu-

Insulin titration schedule for _____		
Change date (when new doses start)	Units of pre-meal rapid-acting analog	Units of peakless insulin glargine (Lantus)
	<input type="checkbox"/> lispro (Humalog) <input type="checkbox"/> aspart (Novolog) <input type="checkbox"/> glulisine (Apidra)	<input type="checkbox"/> Before breakfast <input type="checkbox"/> Before bedtime
	8	24
	10	24
	10	30
	12	30
	12	36
	14	36
	14	42
	16	42
	16	48
	18	48
	18	54
	20	54
	20	60
	22	60
	22	66
	24	66
	24	72
	26	72
	26	78
	28	78
	28	84
	30	84
	30	90
	32	90
	32	96
	34	96

While we are trying to discover the amount of insulin that you need, please eat _____ (gm) (servings) of carbohydrate at every meal. The instruction to eat the same amount at each meal is a temporary restriction. Our goal is to discover the amount of insulin that is needed to get good results for a certain amount of carbohydrate. Then, once we discover the matching rule, you will be free to change the amount that you eat from meal to meal.

Call me if you begin to show any readings under 80 or if you have symptoms of hypoglycemia. If you begin to show some blood glucose readings before meals that are in the target range of _____ to _____ mg/dL, please hold with the dose you are taking, make no further changes of insulin dose, and come in to visit me to review your logbook. Be sure to carry in your meter and one week of logbook glucose readings, marking down what you ate, what insulin you took, and any other information such as unusual exercise.

When we begin to see most readings in the target range, it will be possible to assign a rule for matching the insulin to the amount of carbohydrate at meals. Then you can change the meal size, and match the insulin to the amount of carbohydrate that you would like to eat at any particular meal.

Signed: _____

Date: _____

One serving of carbohydrate (about 15 gm) is found in:

- one piece of bread
- A small piece of fruit
- Half of a large banana
- 4 oz or half a glass of orange juice
- 8 oz glass of milk

Two servings of carbohydrate are found in:

- One cupful or handful of cooked starchy vegetables such as pinto beans, peas, or potatoes

Three servings of carbohydrate are found in:

- One cupful or handful of cooked rice
- One cupful or handful of cooked pasta

cose of 140–199 mg/dl, add 4 units; for blood glucose > 200 mg/dl, add 8 units.

Mary was cautioned to reduce the rapid-acting analog by half if unusual activity was expected to follow the dose of rapid-acting analog within 2–3 hours after injection. Otherwise, for unexpected exercise or for exercise occurring outside the timeframe of action of the rapid-acting analog, she was advised to take 15 g extra carbohydrate (one serving) for every 20 minutes of heavy exercise and not to cover the extra carbohydrate with extra insulin. The consistent carbohydrate requirement was eliminated.

Three months after initiating the basal-prandial-correction regimen, Mary's A1C had fallen 1%. Hypoglycemia was infrequent. Although she still experienced some fluctuation in blood glucose, her logbook showed pre-meal averages in the low 100-mg/dl range without a clear cut upward trend over the course of the day.

Occasionally, Mary performed postprandial testing 1–2 hours after meals to see the effect of her food choices and discovered that some postprandial readings exceeded 200 mg/dl. After a reappointment with the dietitian to review carbohydrate counting with special emphasis on portion size, her postprandial readings seldom exceeded 180 mg/dl and often were < 140 mg/dl.

Questions

1. What blood glucose pattern suggests the need for greater prandial insulin effect?
2. What are the potential advantages of basal-prandial-correction therapy (using rapid-acting analog at each meal and peakless basal insulin) over the use of premixed insulin?
3. How can basal-prandial-correction therapy be initiated and titrated in a primary care setting?
4. How can literacy and numeracy of patients be considered when providing instruction on advanced carbohydrate counting and on use of an insulin-to-carbohydrate ratio to determine the prandial insulin doses?

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Figure 2. One-page handout (front and back) providing patient instructions during initiation of basal-prandial-correction therapy.

Commentary

The case describes a time point in the course of type 2 diabetes at which peakless insulin, combined with daytime oral agents, has failed to achieve satisfactory control.

Patients having type 2 diabetes often fail combination oral therapy and require the addition of insulin. For each of the five major classes of oral agents, successful combination of the oral agent has been reported with use of peakless (glargine) or bedtime NPH insulin. During satisfactory control, the pre meal and postprandial blood glucose should be near target at all times of day, the A1C should be near target, and the patient should have only minimal trouble with hypoglycemia. If a patient has satisfactory control during combination oral therapy with peakless or bedtime NPH insulin, then prandial insulin is not required. Conversely, failure to achieve satisfactory control should suggest the need for intensification, to be achieved potentially by the addition of prandial insulin coverage.

The need for improved prandial coverage may be further suggested by a specific pattern of blood glucose self-monitoring results: progressive rising of blood glucose during the day, with peaking after meals and gradual correction overnight. The first morning blood glucose is the lowest of the day. If a meal delay occurs, there may be hypoglycemia.

The foregoing blood glucose pattern may indicate that any prescribed basal insulin has been prescribed in doses that exceed true basal requirements. The basal insulin is being used to “play catch-up” every night for blood glucose elevations that occurred as a result of eating.

When daytime oral agents, combined with peakless or bedtime NPH insulin, fail to achieve daytime control, the solution often is to replace insulin secretagogue therapy with prandial insulin therapy. At the juncture in a patient’s course at which prandial insulin therapy is added to basal insulin therapy, clinicians

must decide whether to continue or interrupt metformin and thiazolidinedione therapy, based on considerations of cost, patient wishes, and evidence for previous efficacy of the metformin or thiazolidinedione.

One way of delivering prandial insulin is to cover both prandial and basal requirements with intermediate-acting insulin or premixed insulin. Many patients having some endogenous insulin production do reasonably well for a while on such a regimen of premixed insulin.

The use of a rapid-acting analog in comparison to regular insulin,^{1,2} peakless insulin in comparison to NPH,³ and advanced carbohydrate counting in comparison to standard dose therapy⁴ have all been demonstrated in type 1 diabetes to result in improvement of A1C results. Because patients with type 2 diabetes have some endogenous insulin production, the advantages of such therapies in improving A1C may be more difficult to demonstrate. Nevertheless, in type 2 diabetes, the use of peakless insulin in comparison to NPH during prandial use of regular insulin⁵ and the use of a rapid-acting analog in comparison to regular insulin during multiple daily injection therapy⁶ have been shown, respectively, to produce less hypoglycemia and to reduce postprandial hyperglycemia.

In practice, it is because of the problem of hypoglycemia that many patients with type 2 diabetes become frustrated with attempts at intensification. Yet these patients do want to achieve glycemic targets. When offered the option of multiple daily injections, they often say that they are willing to do what is necessary. Despite the requirement for four daily injections, the multiple daily dose treatment plan makes better sense to them than the use of premixed insulin because they understand the purpose of each component of therapy: to cover each meal with a rapid-acting analog, and to provide a peakless insulin to cover between meals and overnight. This is seen as “nature’s way.”

In order to achieve the desired results, many patients with unsatisfactory glycemic control indicate ready willingness to move directly from zero or one to four daily injections of insulin. The use of pen injection devices for prandial coverage makes it easy to include all three meals. Patients are pleased to hear that, while making healthy choices, the end result is the freedom to eat what they like, when they like.⁷

Should clinicians require patients to fail twice-daily injections of premixed insulin before offering the preferred therapy, basal-prandial-correction therapy? To some extent, the answer is determined by patient preference. But to a large extent, unfortunately, the answer is determined by the perceived difficulty of implementing basal-prandial-correction therapy in a busy office practice. There are at least three great stumbling blocks:

1. *Impatience with dose-finding.* At baseline, before starting multiple daily injections, most patients with type 2 diabetes require substantial up-titration of their total daily dose of insulin. However, if there is concern about hypoglycemia, prudence usually requires an initial modest dose reduction from previous insulin therapy, if any was in place. To prevent premature abandonment of the treatment plan, patients need to be forewarned that a period of time will be required during dose titration of insulin before target-range results are seen.
2. *Neglect of prandial insulin up-titration.* Under time pressure during a busy office visit, the path of least resistance is to force the titration of the basal insulin. Neglecting the titration of the prandial insulin leads to lability of control and sometimes to abandonment of the concept of basal-prandial-correction therapy.
3. *Repeated revision of the insulin-to-carbohydrate ratio.* Part of the task of dose discovery is to be sure that the total daily amount of rapid-acting analog remains roughly equal to the amount of basal insulin. To do it

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right, balancing basal and prandial insulin appropriately, one must remain mindful of the average carbohydrate intake of the particular patient. Repeated revisions and restatements of the insulin-to-carbohydrate ratio will confound all but the most adept arithmeticians among our patients. Nevertheless, some practitioners achieve dose titration through repeated revisions of the insulin-to-carbohydrate ratio.

In a primary care practice, implementation of basal-prandial-correction therapy can be achieved easily in five steps (Table 1). The following description applies not only to the situation of transitioning from a single dose of peakless or bedtime NPH insulin, but also from pre-mixed insulin or no insulin to multiple daily injections.

1. *Determine the total daily starting dose of insulin.* For insulin users, the total daily starting dose is 80–100% of the previous daily total insulin dose. For new insulin starts for patients having type 2 diabetes, the total daily starting dose is 0.3 units/kg body weight.
2. *Divide the total daily dose of insulin between peakless insulin and rapid-acting analog.* The insulin should be given half as peakless insulin and half as premeal rapid-acting analog, divided into three parts.
3. *Assign a consistent carbohydrate*

diet. This strategy is a temporary measure to be used during insulin dose titration. Assign an equal amount of carbohydrate for each meal (60 or 75 g for most adults). Many patients prefer to count carbohydrates as servings, each containing ~ 15 g (four or five servings per meal for most adults).

4. *Provide an insulin titration schedule.* Increase peakless insulin and rapid-acting analog in an alternating pattern. Have the patient make a change every third day, as long as all readings are high. For a total daily dose < 48 units, alternate between increasing the rapid-acting analog by 1 unit and increasing the peakless insulin by 3 units. For a total daily dose ≥ 48 units, alternate between increasing the rapid-acting analog by 2 units and increasing the peakless insulin by 6 units.
5. *Instruct on matching insulin to carbohydrate, and eliminate consistent-carbohydrate requirement.* As readings approach target, discontinue forced titration of insulin. Adjust individual component doses of insulin until pattern adjustment is achieved. Evaluate insulin-to-carbohydrate ratios. Instruct the patient on advanced carbohydrate counting and the use of insulin-to-carbohydrate ratios at each meal to determine the dose of rapid-acting analog. Using the insulin-to-carbohydrate ratio and skills of advanced carbohydrate counting, the patient then has freedom to change the carbohydrate content of meals.

Some people have different insulin-to-carbohydrate ratios for each meal. For example, Mary, in our case above, may realize that her supper has more protein and fat than other meals, and that she is less active after supper. However, many patients are best served by a simple rule for a single insulin-to-carbohydrate ratio to be used at any meal. Often, it is best to state only one rule and to be reasonably sure what that rule is before articulating

it to the patient.

Should patients with type 2 diabetes be taught to count carbohydrates by servings or by grams? One carbohydrate serving contains ~ 15 g. Most people eat about three to five servings or 45–75 g of carbohydrate at each major meal and one to two servings or 15–30 g of carbohydrate at snacks. Some centers teach all patients to count by grams, other centers teach all patients to count by servings, and still other centers use either method based on patient characteristics and preference (Table 2).

For most patients, counting by servings is probably easier than counting by grams. Counting by servings requires multiplication or memorization of sequences of numbers together with finger-counting of the number of servings. In the simplest form, counting by servings might be expressed as a memorable rule such as “15 units for three servings, 20 units for four servings, 25 units for five servings.” On the other hand, the use of food labels is more difficult because prior conversion from grams to servings is required. The method of counting by servings is good for relatively high total insulin doses and therefore is good for type 2 diabetes.

When counting by grams, the demands on the quantitative skills of the patient probably are greater than when counting by servings. Counting by grams requires division (sometimes long division). Counting by grams may encourage the use of packaged foods. However, counting by grams is well-adapted for

Table 1. Five Steps to Freedom

1. Determine the total daily starting dose of insulin.
2. Divide the total daily dose of insulin between peakless insulin and rapid-acting analog.
3. Assign a consistent carbohydrate diet.
4. Provide an insulin titration schedule.
5. Instruct on matching insulin to carbohydrate, and eliminate the consistent-carbohydrate requirement.

Table 2. Carbohydrate Counting by Servings and Grams

Servings	Grams
1 unit/serving	1 unit/15 g
1.5 units/serving	1 unit/10 g
2 units/serving	1 unit/7–8 g
3 units/serving	1 unit/5 g
Etc.	Etc.
Multiply number of servings to get number of units.	Divide number of grams to get number of units.

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perfection of care and for use by patients with no endogenous insulin reserve and patients who are sensitive to small differences in insulin dose. Counting by grams allows calculation of fractions of units by users of insulin pumps. Smart pumps may do the math for the patient. Counting by grams often is preferred for insulin-deficient patients.

For unusual exercise planned to occur within 2 hours after administration of rapid-acting analog, patients may be instructed to reduce the rapid-acting dose by 25–50%. For unusual exercise beyond 2 hours after administration, patients may eat one extra 15-g carbohydrate choice for every 20 minutes of exercise (and should not cover the extra carbs with extra insulin).

Correction therapy may be assigned according to the “rule of 1800.” Patients may supplement the pre-meal dose of rapid-acting analog intended to cover the carbohydrate content of the meal with an extra amount intended to correct hyperglycemia. The number 1800 is divided by the approximate total daily dose of insulin to give the drop of blood glucose in mg/dl that 1 unit of rapid-acting analog would produce.

If a preprandial dose of rapid-acting analog already has been given to cover a meal and to correct any preprandial hyperglycemia, and if a correction dose then is added within 2–2.5 hours to correct postprandial hyperglycemia, the patient may experience hypoglycemia for at least two reasons: 1) the correction rule used by the patient may target a preprandial rather than a postprandial blood glucose goal, and 2) the action of the first dose of rapid-acting analog may overlap with the second dose (referred to as “stacking”). To avoid stacking, the use of correction doses should be restricted to premeal timing except on sick days.

It is a common mistake during establishment of basal-prandial-correction therapy to press the dose of the basal insulin to achieve first-morning normoglycemia while neglecting the up-titration

of prandial therapy. The amounts should be about equal. When there is an excessive reliance on basal insulin, lability of control may occur. Upward trending of blood glucose during the day is followed by overnight correction. If meals are delayed, hypoglycemia occurs. Balance may be reestablished by “borrowing from Peter to pay Paul” (i.e., subtracting part of the basal insulin and adding the same number of units to the total daily prandial insulin dose). Depending on the comfort level of the patient, such rebalancing may be achieved all at once or gradually in several steps.

Why bother with such apparent complexity? In reality, multiple daily injection therapy is less complex than the alternative. The necessity to fend off repeated episodes of hyperglycemia and hypoglycemia during fixed dose therapy, without any clear comprehension of what each dose of insulin achieves, is not easy for patients. Basal-prandial-correction insulin therapy quickly becomes intuitive. Each component of insulin therapy has an obvious purpose. Freedom of lifestyle is achieved.

Clinical Pearls

- A pattern of rising blood glucose during the day, with partial or complete correction overnight, suggests insufficient prandial insulin effect.
- In comparison with premixed insulin regimens, basal-prandial-correction therapy (multiple daily injections of insulin) with use of peakless insulin for basal coverage and rapid-acting analog for prandial coverage reduces hypoglycemia and allows greater freedom for patients to eat as they would like while making healthy food choices.
- During dose titration, the basal and total prandial components of insulin therapy should be kept roughly equal in amount.
- When instruction of patients on the use of an insulin-to-carbohydrate ratio

occurs, the individual patient’s needs must be considered.

- Initiation can be achieved with a five-step program.

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Case Study: Glucose Toxicity: Type 1 or Type 2?

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Presentation

J.S. is a 39-year-old male truck driver who presented to the emergency room (ER) on a Friday night complaining of polyuria, polydipsia, and fatigue of 2 weeks' duration. He also reported a 15- to 20-lb. weight loss over the past 1–2 months. He denied any antecedent acute illness and had not been diagnosed with any chronic medical conditions. He had no known allergies and was taking no medications.

The patient's mother died at age 75 with Alzheimer's disease and alcoholic cirrhosis. His father died from prostate cancer at age 79. There was no family history of diabetes, hypertension, or heart disease. He reported smoking a half-pack of cigarettes per day, drinking 1–2 beers nightly, and bingeing with two 12 packs of beer on most weekends.

J.S. weighed 228 lb. (104 kg) and is 5'11" in height. His BMI is, therefore, 32 kg/m². He was afebrile, and his blood pressure was 132/82 mmHg. His physical exam was remarkable only for signs of mild dehydration.

The patient's serum test results were as follows: glucose, 682 mg/dl; sodium, 131 mEq/l; potassium, 3.6 mEq/l; CO₂, 25 mEq/l; creatinine, 1.4 mg/dl; ketones, negative; and hemoglobin A_{1c} (A1C), 11.7%. His hepatic chemistries were normal. Urine ketones were 40 mg/dl, and urine glucose was > 1,000 mg/dl.

In the ER, J.S. received intravenous insulin and fluids. After 5 hours, his serum chemistries were as follows: glucose, 270 mg/dl; sodium, 137 mEq/l; potassium, 3.0 mEq/l; creatinine, 1.1 mg/dl; and CO₂, 23 mEq/l. He was discharged from the ER with a prescription

for rosiglitazone, 4 mg daily, and was instructed to see his family doctor for follow up of newly diagnosed diabetes.

Three days later, at his initial family practice visit, J.S. reported improvement in his diabetes symptoms. He had taken rosiglitazone daily and had purchased a home blood glucose monitoring device. His capillary glucose was 308 mg/dl, urine glucose was > 1,000 mg/dl, ketones were 40 mg/dl, albumin/creatinine ratio was 6.0 mg/g, serum insulin was 8.0 uU/dl (normal range: 3.0–25.0 uU/dl), and serum ketones were negative.

J.S. was instructed by a diabetes nurse educator in basic diabetes nutrition principles, exercise goals, home blood glucose monitoring techniques, insulin administration, and sick day management guidelines. A metformin/glyburide combination pill, 2.5 mg/500 mg twice daily, was added as well as glargine, 15 units at bedtime. The treating physician was not sure whether J.S. had type 1 or type 2 diabetes.

Six days after diagnosis, J.S. presented blood glucose records with most values ranging between 250 and 350 mg/dl before meals. His in-office blood glucose reading 30 minutes after breakfast was 265 mg/dl, and his urine ketones were negative. He reported definite adherence to nutrition recommendations, alcohol avoidance, and exercise, as well as compliance with medication dosing.

His glargine dose was increased to 20 units and his metformin/glyburide was increased to 5 mg/1,000 mg twice daily. Aspart supplemental insulin dosing was added premeal when his blood glucose level was ≥ 151 mg/dl and

increased by 1 unit for each 50 mg/dl increment > 150 mg/dl.

J.S. had stopped smoking and had been taking aspirin, 81 mg/day. He was aware that he could not legally return to work as an interstate tractor-trailer driver because federal law prohibits insulin-using people with diabetes from interstate driving.

By his next office visit 11 days after diagnosis, J.S. had reduced his glargine dose to 15 units and had stopped using aspart. His blood glucose values were all < 140 mg/dl. Urine tests for glucose and ketones were negative. The doctor agreed with his request to stop taking glargine and aspart insulins. Because he had carefully followed all of his provider's recommendations, he was able to return to work driving a truck. He agreed to test his blood glucose 4–6 times/day, eat meals at 4- to 5-hour intervals, and report to the doctor's office by phone or office visit weekly.

At 3 weeks after diagnosis, J.S.'s blood glucose log revealed all tests in the 70- to 137- mg/dl range. His metformin/glyburide was discontinued. Metformin, 1,000 mg twice daily, and repaglinide, 2 mg before meals, were prescribed. The intent of substituting a short-acting meglitinide for a long-acting sulfonylurea was to decrease the likelihood of between-meal hypoglycemia. J.S. denied any hypoglycemic symptoms or low blood glucose values while driving.

At 4 months, his A1C result was 6.1%. At 7 months, his A1C was 5.1%, and his serum insulin level had risen to 44.5 uU/dl. His total cholesterol was 191 mg/dl, triglycerides were 249 mg/dl,

HDL cholesterol was 37 mg/dl, and LDL cholesterol was 104 mg/dl.

Questions

1. Did J.S. present in the ER as a type 1 or type 2 diabetic patient?
2. What may have precipitated his severe hyperglycemia and ketonuria?
3. If J.S. continues his excellent self-management of diabetes, what is likely to be his greatest long-term health risk?

Commentary

When J.S. presented in the ER, he met most criteria for diagnosis of type 1 diabetes. His fatigue, rapid weight loss, dehydration, severe hyperglycemia, and ketonuria all could have been interpreted as new-onset type 1 disease. ER management with fluid replacement and intravenous insulin resulted in rapid improvement in hydration, with reduction of glucose from 682 to 270 mg/dl. However, the ER physician must have been thinking the diagnosis was type 2 disease, since he discharged the patient with a prescription for rosiglitazone, 4 mg daily. (The physician may not have been aware that the thiazolidinedione class of medications requires several weeks to significantly reduce insulin resistance in muscle, fat, and hepatic tissues.)

The family practice office follow-up revealed continued failure to adequately reduce hyperglycemia and ketonuria with additional oral therapies. Within 1 week of initiating insulin, blood glucose values were < 140 mg/dl; insulin therapy was stopped and sulfonylurea treatment was begun. After another week, this was changed to the meglitinide repaglinide, which he had only rarely used subsequently.

J.S. presented with severe glucose toxicity. In this condition, prolonged hyperglycemia impairs glucose-stimulated insulin secretion by pancreatic β -cells and impairs glucose disposal by muscle, fat, and liver. His alcoholic binge-drinking on weekends may have

also contributed to high free fatty acid levels that also impair insulin secretion and sensitivity.^{1,2}

Glucose toxicity can be corrected quickly (within days), especially in recently diagnosed type 2 diabetic patients. Aggressive insulin treatment, with the goal of returning patients to near-normoglycemia, is the most effective method of achieving this goal. Once this is achieved, less aggressive therapies of diet, exercise, insulin sensitizing medication, and/or medications that stimulate insulin secretion may be sufficient to maintain good blood glucose control for prolonged periods.

More gradual reduction of glucose toxicity can be achieved by weight reduction. However, when blood glucose is consistently > 300 mg/dl, the patient is symptomatic, and use of insulin is usually required to return the patient to a physiological state that responds to hyperglycemic stimuli with endogenous insulin secretion.³

J.S.'s 7-month A1C, insulin level, and lipid profiles reflect values consistent with well-controlled type 2 diabetes. Attention still must be given to reducing his cardiovascular risk profile, including smoking cessation and improvement in lipid values.

J.S. reports that he has ceased using alcoholic beverages. Because of his family history, alcohol abuse will remain a major risk to his life and well being. Frequent inquiries about his tobacco and alcohol use will demonstrate concern and openness to address these risks. Supportive and referral therapies should be offered when indicated.⁴

Clinical Pearls

- Glucose toxicity occurs frequently in type 2 diabetes. When profound hyperglycemia (blood glucose > 300 mg/dl) is persistently present, pancreatic β -cell insulin release is downregulated. In the presence of underlying insulin resistance, this contributes to progressively greater hyperglycemia and may lead to ketosis.

- Glucose toxicity can be reversed by aggressive treatment of severe hyperglycemia with insulin. The goal is to return blood glucose to near-normal values for several days or weeks to allow restoration of islet-cell insulin production. When this occurs, then diet, exercise, and oral antidiabetic medications may be sufficient to allow the patient to maintain near-normalization of blood glucose for extended periods of time.
- Alcohol abuse can contribute to the symptoms of glucose toxicity. Alcoholism prevention and intervention should be as much of an issue for patients such as J.S. as prevention of diabetes complications. Open discussion and appropriate referral should be considered at office visits.

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Case Study: Man With Type 2 Diabetes and Stage 1 Kidney Disease on Atkins-Like Diet

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Presentation

C.S. is a 45-year-old Hispanic man with a 10-year history of type 2 diabetes. He has a glycated hemoglobin of 7.0% and a blood pressure of 130/80 mmHg, treated with an angiotensin-converting enzyme inhibitor for the past 2 years. He has stable background retinopathy and is a nonsmoker. His BMI has been 30 (height 5'10", weight 210 lb) for the past year. However, lately, he has put himself on the latest high-protein diet (i.e., the Atkins diet).

His weight has dropped by 10 lb, his fasting serum triglyceride level has fallen from 185 to 130 mg/dl, and his blood pressure has decreased to 120/78 mmHg. His LDL cholesterol has remained stable at 102 mg/dl on a statin. His serum creatinine is 0.9 mg/dl, and his 24-hour urine shows a significant increase in microalbuminuria from 100 mg/24 hours last year to the current 200 mg/24 hours. He has stage 1 chronic kidney disease indicating kidney damage, with a normal glomerular filtration rate (GFR) of 98 ml/min/1.73 m².

Questions

1. Would the weight reduction, blood pressure, and lipid-lowering accomplished by this high-protein, low-carbohydrate diet be an acceptable choice for a patient who is at significant risk of cardiovascular disease?
2. What are the recommendations of the American Heart Association (AHA), the National Kidney Foundation (NKF), the National Academy of Sciences, and the American Diabetes Association (ADA) regarding this type of diet for

diabetes and/or weight loss?

3. What has research revealed about appropriate levels of macronutrients for patients such as C.S.?

Commentary

It is likely that microalbuminuria is the start of a continuum progressing to macroalbuminuria and proteinuria. Microalbuminuria predicts renal disease in diabetes (both type 1 and type 2) and relates to premature mortality. Microalbuminuria is also a marker for pronounced diabetic vascular disease (endothelial dysfunction and chronic low-grade inflammation). Abnormal albuminuria is a major risk factor for cardiovascular complications, predicting increased cardiovascular morbidity and mortality.¹

Twenty to thirty percent of patients with type 2 diabetes develop evidence of nephropathy. Some patients already have microalbuminuria or overt nephropathy upon diagnosis. Without intervention, 20–40% of those with microalbuminuria progress to overt nephropathy. For those on the continuum from overt nephropathy to end-stage renal disease (ESRD), the greater risk of death from coronary artery disease (CAD) may intervene.²

The average adult protein intake in the United States is 15–20% of total calories and has remained consistent from 1909 to the present.³ Most Americans eat 50% more protein than they need. The Recommended Dietary Allowance (RDA) is 0.8 g of good quality protein per kilogram body weight per day for men and women. The high-protein Atkins and Zone diets recommend 125 g/day (36% kcal from protein) and

127 gm/day (34% kcal from protein), respectively.⁴ The initial phases of the South Beach diet are similar, but no specific nutrient intake can be found in the diet's literature. In C.S., the Atkins diet would contribute 1.3 g protein/kg body weight and 36% of total daily calories from protein. Thus, high-protein diets promote a significantly abnormally high protein intake.

There is some evidence that a sustained high-protein diet can adversely affect renal function, especially in people with diabetes with or without mild renal insufficiency. In patients without renal insufficiency, a high-protein diet may act by acutely increasing the GFR and causing intraglomerular hypertension, which may cause progressive loss of renal function. In the Nurses Health Study, 1,624 female nurses between 30 and 55 years of age were followed for a period of > 11 years. The highest quartile of total protein intake, an average of 93 g/day, was significantly associated with a decline in GFR in women with mild renal insufficiency, thus worsening renal disease.⁵ Previous studies had shown mixed results of high-protein diets on renal function but had limitations such as small patient numbers, limited follow-up, and a narrow range of protein intake.

Looking at this relationship from another angle, a meta-analysis recently showed that protein restriction retards the rate of decline in GFR, thus lessening kidney damage. The resulting decrease in kidney damage was small and not impressive. However, when studies looking at people with diabetes were combined, a total of 102 patients

given a mean protein restriction of 0.7 g/kg/day versus a control group given 1 g/kg/day (a narrow range), showed a more impressive improvement in renal function independent of the original renal function over 22 months.⁶ A cross-sectional study of > 2,600 people with type 1 diabetes found that a protein intake > 20% of calories was associated with an increased urinary albumin excretion rate. Researchers concluded that people with diabetes should not exceed a protein intake of 20% of calories.⁷ Any study in type 1 diabetes is applicable to type 2 diabetes as it relates to nephropathy. Therefore, there is evidence to recommend avoidance of high protein intakes in patients at risk for renal disease, i.e. all patients with type 1 or type 2 diabetes.

Nutrient analysis of high-protein diets is a concern. With some high-protein diets, such as Atkins, come carbohydrate restrictions. Yet high-carbohydrate foods, such as fruits, vegetables, and low-fat dairy products, provide potassium, magnesium, and calcium, which modestly reduce blood pressure.⁸ Normal blood pressure is critically important in preventing CAD and microalbuminuria. With high-protein diets and carbohydrate restrictions come decreased-fiber diets. High-fiber diets have many beneficial effects, including weight loss and lower cardiovascular and cancer risks. With high-protein diets come higher intakes of saturated fats, which are potentially atherogenic.⁹ In addition, experimental evidence indicates that a high-protein diet and the resultant increase in saturated fat intake may accelerate the progression of renal disease. Increased LDL cholesterol can stimulate mesangial hypertrophy and stimulate cytokine formation, which may ultimately cause tissue injury. In both type 1 and type 2 diabetes, hypercholesterolemia is a predictor of deteriorating kidney function.¹⁰

The RDA for carbohydrate is set at 130 g carbohydrate/day for adults and children based on the average minimum amount of glucose utilized by the brain

to ensure optimal brain function.¹¹ That pretty much omits Atkins (28–33 g/day) and the early phases of the South Beach diet. Recent AHA guidelines discourage high-protein diets for weight loss, citing potential increased risk for coronary heart disease and renal disease.¹² The most recent ADA technical review on nutrition states that high-protein diets are not recommended until further research establishes their safety.³ Concerns include renal function and cardiovascular disease. The NKF states in its Kidney Disease Outcomes Quality Initiative guidelines for chronic kidney disease that there is no benefit from a protein intake higher than the RDA of 0.8 g/kg body weight and that this is a reasonable level to recommend for patients with chronic kidney disease in stages 1–3.¹³ Thus, many respected nonprofit health care organizations discourage the use of high-protein, low-carbohydrate diets.

Literature reviews of research on the effect of high-protein, low-carbohydrate diets on obesity and lipid levels are not convincing. A review of the literature describing adult outpatient recipients of low-carbohydrate, high-protein diets compared a wide variety of study designs, carbohydrate levels, durations, and calorie levels. Only five studies evaluated low-carbohydrate, high-protein diets for > 90 days, and these were non-randomized, uncontrolled studies. The three variables that most predicted weight loss were calorie level, duration of calorie restriction, and number of very obese participants in the study. Reduced carbohydrate content was not significantly associated with weight loss.¹⁴

Another review concluded that populations at risk for renal disease, such as patients with diabetes, should avoid high-protein diets. The authors also caution that evidence suggested that protein intakes in excess of two to three times the RDA may have harmful effects on calcium homeostasis and possibly bone mass,¹⁵ a problem for a population already predisposed to osteoporosis. In addition, a comparison of high-protein, low-carbohydrate diets versus a low-fat

diet for weight loss shows them equally effective after 1 year in duration.¹⁶ A recent small, randomized, clinical trial comparing a low-carbohydrate (< 30 g) to a conventional low-fat diet in severely obese patients, including individuals with diabetes, showed no significant difference in weight loss after 1 year, although weight loss was minimal (11 vs. 7 lb). Of interest was that the weight loss on the low-carbohydrate diet did not appear to be sustainable and that blood urea nitrogen levels increased more in the low-carbohydrate group.¹⁷

Reduced energy intake is an important therapeutic objective for the patient in the case described above. Reduced energy intake would reduce his blood pressure and serum lipids as well as improve his glycemic control. Weight loss was effective in lowering his blood pressure and serum triglycerides, as one would expect. However, the macronutrient content of his diet may have exacerbated the microalbuminuria. Therefore, a patient such as C.S. would be ill-advised to stay on the high-protein diet because of the potential risk to his kidney function as shown by his elevated microalbuminuria.

With guidance from a registered dietitian, C.S. started a 1,500-kcal, low-fat diet with a walking program of 2 miles/day, 6 days/week. He was very tired of the restrictive nature of the high-protein diet and welcomed a change. His urine microalbumin level fell to < 50 mg/24 hours.

Two important studies show strategies that work to yield long-term weight loss. In order to determine what strategies work for long-term weight loss, the National Weight Control Registry elicited and studied information from > 800 people who have been successful in this endeavor. Only half had lost weight through weight loss programs. The remainder had lost weight without medical intervention. Keys to success were an average calorie intake of ~ 1,400 kcal/day, a low-fat diet (24% of kcal), and a high energy expenditure through exercise (2,800 kcal/week).¹⁸ The Dia-

betes Prevention Program also documented that a low-fat diet, increased physical activity, and educational sessions with frequent follow-up allowed participants to lose 7% of their body weight and maintain a 5% weight loss for 3 years.¹⁹

Clinical Pearls

- High protein intakes cause higher workloads for kidneys, whose function is to handle amino acid fragments during protein degradation and excrete nitrogen as urea.
- There is no research documenting that a high-protein diet maintains weight reduction any better than a low-fat diet, which is safer and offers long-term results.
- Safety and efficacy of high-protein, low-carbohydrate diets are a concern for patients with diabetes, regardless of documented kidney disease.

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Additional Information

Concerns about the low-carbohydrate diet craze of 11 leading nonprofit consumer, nutrition, and public health organizations are discussed in a format appropriate for both health professionals and patients at the Partnership for Essential Nutrition website: www.essentialnutrition.org.

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