Metformin has remained the cornerstone of therapy for patients with type 2 diabetes mellitus (T2DM) who do not have contraindications to its use and who can tolerate it. Metformin’s widespread use is based on its glucose-dependent mechanism of action (with a low risk of hypoglycemia), its lack of association with weight gain, its durability of effect, its long history of safety, and its generic availability.¹
In addition, metformin may have beneficial effects in reducing cardiovascular risks\(^2\) and cancer risks\(^3\) in patients with T2DM.

Traditionally, sulfonylureas (ie, insulin secretagogues) or thiazolidinediones (ie, insulin sensitizers) were among the only other available oral treatment options for individuals with T2DM. In recent years, however, a new generation of oral and injectable antidiabetic therapies—besides insulin—became available.\(^4\) Now the clinician is faced with many more treatment options and many more safety, efficacy, and tolerability issues to consider when personalizing treatment for patients who require combination therapy in addition to metformin as T2DM progresses.

In the present article, I focus on a rationale for the use of glucagon-like peptide-1 (GLP-1) receptor agonists as add-on therapy to metformin for some patients with T2DM.

Case report

Julia is a 48-year-old woman with T2DM who presents to a primary care physician complaining of weight gain. She understands that, as an individual with diabetes mellitus, she needs to try to maintain a healthy weight to assist in attaining glucose control. She was diagnosed with T2DM 3 years ago, as she went through menopause. A year before this diagnosis, she could not understand why she was gaining weight, despite exercising a few times per week. After the diagnosis, she began metformin therapy and saw a nutritionist. She learned to perform self blood glucose monitoring and to test fasting plasma glucose (FPG) levels daily. She was pleased that she was able to lose 3 pounds and attained a glycosylated hemoglobin (HbA\(_1c\)) level of 6.2% after 6 months. Her body mass index (BMI) at that time was 31. For the next 18 months, she maintained a healthy lifestyle and an FPG level below 130 mg/dL, as recommended by her family physician.

Initial therapy: lifestyle intervention plus pharmacotherapy

Typically, therapeutic strategies for patients with T2DM begin with diet and exercise modification, followed by the gradual and sequential addition of medications. The current treatment paradigm acknowledges intrinsic physiologic defects present early in the course of the disease that require efforts beyond lifestyle modification alone, including pharmacologic therapy, with metformin most often being used as the initial therapy (in the absence of contraindications).\(^1,5\) Metformin has become the cornerstone of therapy on the basis of its efficacy, low risk of hypoglycemia, low risk of weight gain, and generic availability.

When treatment goals are not achieved or maintained with metformin and lifestyle modification, treatment should be promptly intensified to combination drug therapy using agents with complementary mechanisms of action. In addition, lifestyle intervention (eg, physical activity, healthy eating, nonuse of tobacco, weight management, effective coping) should be continued and even intensified as the disease progresses.\(^1,5\) Other recommendations for improving the care of patients with diabetes mellitus include the following:6

- Explore patient’s goals for treatment.
Set explicit goals with patients.
Identify and address barriers to care.
Integrate evidence-based guidelines into care.
Incorporate care management teams.
Implement a systematic approach to support patients’ efforts at behavioral changes.
Incorporate disease self-management, including medication taking and management and self-monitoring of glucose levels and blood pressure when clinically appropriate.
Prevent disease complications through self-monitoring of foot health; patient participation in screenings for eye, foot, and renal complications; and immunizations.

**Lifestyle modifications**

The Centers for Disease Control and Prevention has documented the dramatic simultaneous increase in prevalence of diabetes mellitus and obesity in the United States (Figure 1).

Lifestyle modification, primarily calorie reduction and appropriate physical activity, remains the cornerstone of control of obesity in patients with T2DM. Ongoing therapeutic lifestyle management should be discussed with all patients with diabetes mellitus throughout their lives. Medical nutritional therapy must be individualized, generally requiring evaluation and teaching by a trained nutritionist/registered dietitian or a knowledgeable physician. In addition to proper nutrition and physical activity, lifestyle management includes the avoidance of tobacco products and the promotion of an adequate quantity and quality of sleep.

Regular physical activity, that includes both aerobic exercise and strength training, is important to improve a variety of cardiovascular disease risk factors, to decrease the risk of falls and fractures, to improve functional capacity, and to improve glucose control in individuals with T2DM. Recommendations for at least 150 minutes per week of moderate-intensity exercise, such as brisk walking or its equivalent, are now well accepted and part of national guidelines. The main

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**Figure 1. The simultaneously increasing rates of obesity**
The simultaneously increasing rates of obesity and diabetes mellitus from 1994 to 2009, shown according to the percentages of adults with these conditions in each state.

*Source: Centers for Disease Control and Prevention, National Diabetes Surveillance System.*

physical activity recommendations for patients with diabetes mellitus are as follows:

- Advise patients to perform at least 150 minutes per week of moderate-intensity aerobic physical activity (ie, 50%-70% of maximum heart rate), spread over at least 3 days per week with no more than 2 consecutive days without exercise.

- In the absence of contraindications, patients should be encouraged to perform resistance training at least twice per week.

  Four-year results from the Look AHEAD trial show that comprehensive lifestyle intervention can induce clinically significant weight loss (ie, ≥ 5%) in overweight or obese participants with T2DM. This weight loss was maintained in more than 45% of the patients in the trials. Intentional weight loss is known to decrease the need for antidiabetic medications, primarily by improving insulin resistance.

**Pharmacotherapy**

At Julia’s next 3-month checkup, her FPG level mean increased to 160 mg/dL, and her HbA1c level was found to be increased to 7.4%. Glimepiride 2 mg daily was added to
metformin 1000 mg twice daily. Her glucose reading improved, however she quickly learned that if a meal was delayed, hypoglycemia would ensue. Within another 3 months, her HbA1c level was again below 7%, but she had gained 5 pounds. She had also curtailed exercise somewhat because of her fear of hypoglycemia.

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have recently updated their recommendations for the management of hyperglycemia to take a more holistic approach, encouraging the individualization of treatment goals and options for patients with diabetes mellitus. As previously mentioned, most patients with T2DM begin pharmacotherapy with metformin, but they eventually need additional medications. Figure 2 summarizes possible progressions in therapy after metformin and before the full use of basal bolus insulin.1 If the patient’s HbA1c target is not achieved after approximately 3 months of lifestyle treatments and metformin, 1 of these 5 treatment options should be considered: metformin combined with (1) a sulfonylurea, (2) a thiazolidinedione (TZD), (3) a dipeptidyl peptidase-4 (DPP-4) inhibitor, (4) a GLP-1 receptor agonist, or (5) basal insulin. The choice is based on patient and drug characteristics, with the overriding goal of improving glycemic control while minimizing adverse effects. Shared decision-making with the patient may help in the selection of therapeutic options.1 Figure 3 summarizes key benefits and risks of the main classes of antidiabetic medications.9

**Limitations of insulin secretagogues**

One of the biggest concerns with sulfonylureas is hypoglycemia. Medication associate hypoglycemia is likely under-recognized and under-reported as a cause of morbidity and mortality.10-12 Hypoglycemia adversely affects patients’ quality of life and may influence adherence to treatment—and, thus, the success of the treatment.13,14 Patients and their friends, families, and neighbors should be educated about the signs and symptoms of hypoglycemia and its treatment.15

The use of sulfonylureas results in a relatively rapid lowering of glucose levels. However, the use of these agents is not always successful in maintaining glucose control over the long-term. The progressive β-cell failure seen in T2DM results in even-

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**Figure 3. Key benefits and risks of antidiabetic medications**

Key benefits and risks of antidiabetic medications: metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, sulfonylureas, thiazolidinediones, and insulin. Abbreviation: CHF, congestive heart failure.9

Source: Endocrine Practice: official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists, by American College of Endocrinology; American Association of Clinical Endocrinologists, Copyright 2012. Adapted with permission of Aacecorp Inc.
tual loss of sulfonylurea efficacy, which depends on the number of remaining β-cells. Therefore, sulfonylureas are ineffective in the absence of insulin-producing capacity. This limitation was demonstrated in the ADOPt study, which assessed the “durability” of glucose-lowering effects among metformin, TZDs, and sulfonylureas. Sulfonylureas had the least durability, and TZDs had the most durability.

Hypoglycemia is a major concern with the use of either sulfonylureas or insulin. The association between these agents and hypoglycemia was a perceived disadvantage of the previous treatment algorithm issued by the ADA and EASD. That algorithm did not take a holistic approach with patients and did not incorporate ambient HbA1c levels, possible contraindications, or risks of weight gain or hypoglycemia into treatment choices. In the revised ADA/EASD algorithm, the use of sulfonylureas is not encouraged if avoidance of hypoglycemia is the main objective of therapy.

Twelve months after starting glimepiride, Julia’s HbA1c level was again elevated, to 7.7%, her FPG level was 170 mg/dL, and she had gained another 5 pounds, increasing her weight to 180 pounds and her BMI to 32. She was frustrated and depressed. When injectable therapy was mentioned, Julia quickly refused. Nevertheless, her family physician discussed the advantages of injectable therapy using a GLP-1 receptor agonist. The 2 major advantages were attainment of glycemic control with the possibility of weight loss. Adverse effects include possible transient nausea and the potential risk of pancreatitis. The risk of Medullary thyroid tumors (a very rare thyroid cancer), as noted in rodents, was also discussed with the patient.

**Limitations of thiazolidinediones**

TZDs have been available for some time and appear to be durable and address insulin resistance in diabetes. But these agents are being used less often. With recent concerns about the short-term tolerability (eg, weight gain, fluid retention) and long-term safety (eg, risk of osteoporosis, possible association with bladder cancer) of TZDs, the advantage of durability alone may not be enough to support the use of pioglitazone in addition to, or as a replacement for, a sulfonylurea.

**Increasing role of incretin-based therapies**

A distinct advantage of incretin-based therapies—both oral DPP-4 inhibitors and injectable GLP-1 RAs—is that they work in a glucose-dependent manner (ie, only when glucose levels are high). Thus, incretin-based therapies are associated with a very low risk of hypoglycemia, unless they are used with agents that work in a glucose-independent manner—which is the reason that doses of sulfonylureas and insulin may need to be lowered if a GLP-1 RA is used with these agents.

Although DPP-4 inhibitors are weight neutral, GLP-1 RAs are associated with a slow, progressive (and dose-dependent) loss in weight, primarily a loss in adipose tissue. Given Julia’s frustration with weight gain, despite her efforts at lifestyle modification, and her concerns about hypoglycemia, the use of 1 of the available GLP-1 receptor agonists (ie, exenatide twice daily, liraglutide once daily, or exenatide extended release once weekly) is a reasonable therapeutic option. Both the ADA/EASD algorithm and that of the American Association of Clinical Endocrinologists (AACE) encourage the use of incretin-based therapies in patients for whom weight gain is problematic and for whom avoiding hypoglycemia is important.

**Figure 4** compares and contrasts DPP-4 inhibitors and GLP-1 receptor agonists.
GLP-1 RAs. Figure 5 summarizes features of the available GLP-1 receptor agonists, including mechanisms, actions, advantages, and disadvantages.6

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<tr>
<td>Mechanism</td>
<td>Activates GLP-1 receptors (β-cells/endocrine pancreas; brain/autonomic nervous system)</td>
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<tr>
<td>Action(s)</td>
<td>Insulin secretion up (glucose-dependent)</td>
<td>Glucagon secretion down (glucose-dependent)</td>
<td>Slows gastric emptying</td>
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<td>Advantages</td>
<td>Low hypoglycemia risk</td>
<td>Weight reduction</td>
<td>Improvement in cardiovascular risk factors</td>
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<td>Disadvantages</td>
<td>Gastrointestinal adverse effects (nausea, vomiting, diarrhea)</td>
<td>Cases of acute pancreatitis observed</td>
<td>C-cell hyperplasia/medullary thyroid tumors in animals (liraglutide, exenatide extended duration)</td>
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<td>Cost</td>
<td>High</td>
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Figure 5. Summary of features
Summary of features of available glucagon-like peptide-1 (GLP-1) receptor agonists, including mechanisms, actions, advantages, and disadvantages. Adapted with permission from Diabetes Care.6

GLP-1 RAs.26,27 Figure 5 summarizes features of the available GLP-1 receptor agonists, including mechanisms, actions, advantages, and disadvantages.6

Glucagon-like peptide-1 receptor agonists

Efficacy when added to oral antidiabetic monotherapy

Given the combination of effective glycemic control and weight benefits, addition of a GLP-1 receptor agonist may be a good option for early add-on therapy for patients receiving oral antidiabetic monotherapy, such as Julia. For example, for patients receiving metformin monotherapy, the addition of either liraglutide or glimepiride was shown to result in similar levels of glycemic control, though patients receiving glimepiride had statistically significant greater weight gain ($P<.001$) and higher rates of minor hypoglycemia.28 Comparisons of liraglutide vs sitagliptin in patients not achieving adequate glycemic control with metformin monotherapy showed that liraglutide offered sustained, more effective glycemic control and weight reduction compared to sitagliptin.29,30 In addition, liraglutide was also associated with greater treatment satisfaction (independent of effects on weight) at 1 year after treatment initiation.29,30 Likewise, in trials lasting longer than 1 year, exenatide twice daily was generally well tolerated, producing a durable reduction in HbA1c levels and a progressive reduction in weight in patients with T2DM.31 In patients taking metformin, exenatide twice daily was comparable to the use of premixed insulin for glycemic control, and it was better in terms of hypoglycemia and weight control.32

The recently approved long-acting formulation of exenatide (exenatide extended duration), which is given once weekly, was more effective than a TZD or DPP-4 inhibitor as an adjunct to metformin in achieving a combined endpoint of optimum glucose control with weight loss—without hypoglycemia.33

Precautions and contraindications

If an incretin-based medication is selected it is important to review the safety issues with the patient. Prescribing information states that incretin-based medications (both DPP-4 inhibitors and GLP-1 receptor agonists) should be stopped if “signs of pancreatitis” develop (eg, persistent abdominal pain that can radiate to the back, with or without nausea and vomiting), and that these agents should not be used in patients who have a history of pancreatitis.18,34-36 Diabetes mellitus and obesity, in and of themselves, increase the risks of pancreatitis, and available data do not suggest a difference between the incidence of pancreatitis in patients using incretin-based therapies vs other classes of glucose-lowering agents.37 Julia was counseled about the symptoms of pancreatitis and advised to call her physician should she experience these symptoms.

Liraglutide and exenatide extended-release are contraindicated in patients who have rare forms of thyroid cancer (eg, multiple endo-
Crine neoplasia syndrome type 2) or a personal or family history of medullary thyroid cancer. Serum calcitonin is a well-accepted marker of C-cell proliferation, particularly in medullary thyroid carcinoma. Long-term administration of GLP-1 receptor agonists in rodents has been associated with increased serum calcitonin levels and C-cell tumor formation. However, recent data do not support an effect of GLP-1 receptor activation on serum calcitonin levels in humans. Thus, concerns based on rodent studies may not apply to humans. Nevertheless, the long-term consequences of treatment with GLP-1 receptor agonists will remain a subject of further studies. In any event, patients should be counseled to contact their physicians if they have a lump or swelling in the neck, hoarseness, trouble swallowing, or shortness of breath, because these conditions may be signs of thyroid cancer.

**Treatment initiation**

After this discussion, both Julia and her physician agreed—the advantages of GLP-1 receptor agonists outweighed the risks. Julia was shown the pen injection device and potential injection sites, and she began liraglutide treatment with the initiation dose of 0.6 mg. This dose was to be taken once daily in either the morning or evening independent of meals. Julia was told that the same time frame should be maintained for the injection. Assuming no severe nausea after 1 week, the dose was to be increased to 1.2 mg and maintained until the patient’s next visit. If nausea was noted after the initiation dose, that dose was to be maintained until the nausea abated. To alleviate the risk of hypoglycemia, the patient’s dose of glimepiride was decreased to 1 mg daily. To ensure safety, she was asked to test her glucose level a second time before dinner—a time point when hypoglycemia was previously common.

Julia started taking liraglutide in the morning, soon after she awakened. Nausea was not an issue, so she increased the dose to 1.2 mg after the first week. She noted a feeling of satiety, though she believed that she was eating less. When she returned to her family physician 3 weeks after beginning liraglutide, her FPG level was found to be decreased, to 140 mg/dL. In addition, the occurrence of her daytime hypoglycemia was reduced, though it still occasionally occurred before dinner. Her family physician asked Julia to increase the liraglutide dose to 1.8 mg/dL and to stop the glimepiride altogether.

**Patient follow-up**

With the increase in liraglutide dose to 1.8 mg/dL and the cessation of glimepiride, Julia noted FPG values between 120 and 130 mg/dL and pre-dinner glucose values of 80 to 100 mg/dL, as well as the disappearance of hypoglycemia and the need to snack to prevent hypoglycemia. Three months after the increase in liraglutide dose, Julia’s HbA1c level was 6.9% and she had lost 8 pounds.

Julia has returned to the gym 3 times a week, and she now feels back in control to manage her diabetes mellitus.

**Key Learning Points**

- Nutrition, physical activity, and patient education constitute the foundation of any treatment program for patients with T2DM.
- Unless contraindicated, metformin is a cornerstone of antihyperglycemic therapy.
- Many patients will require medications in addition to metformin to either achieve or maintain glycemic control.
- Treatment decisions should be made in conjunction with the patient, focusing on the patient’s needs and preferences.
- The GLP-1 receptor agonists may be an attractive treatment option because of their glucose-lowering efficacy, their association with weight loss, and their low risk of hypoglycemia in patients who are willing to use injectable agents.
**Are GLP-1 receptor agonists like insulin?**

Although both GLP-1 agonists and insulin are administered by means of subcutaneous injection and are relatively potent in their glucose-lowering effects, they differ in several important respects. Most importantly, unlike insulin, GLP-1 receptor agonists are associated with a very low risk of hypoglycemia. Patients can be reassured that these agents work only when glucose levels are high. In contrast to the use of insulin therapy, which is often associated with weight gain, the use of GLP-1 receptor agonists to manage hyperglycemia may have the additional benefits of lowering body weight, systolic blood pressure, and triglyceride levels—all of which may be elevated in patients with T2DM.

Clinical trials comparing GLP-1 receptor agonists with insulin have shown that GLP-1 receptor agonists lower blood glucose levels to levels similar to when insulin is administered, but with less weight gain and hypoglycemia.[32,40,41] In addition, treatment satisfaction has been reported to favor GLP-1 receptor agonists over insulin, independent of weight effects.[42]

**Availability, dosage, and administration**

Liraglutide is available as pen sets, with each pen delivering a dose of 0.6 mg, 1.2 mg, or 1.8 mg. Patients will use 2 pens per month at a dosage of 1.2 mg daily and 3 pens per month at a dosage of 1.8 mg daily. Patients may administer injections at any time of day, independent of mealtimes, but preferably at the same time each day. The starting dosage is 0.6 mg daily, which is not a clinically effective dose but rather a dose to acclimate the patient to possible gastrointestinal adverse effects (eg, nausea, vomiting). If tolerated, the starting dosage is increased to 1.2 mg daily. Some patients may require further dosage escalation to 1.8 mg daily; glucose-lowering and weight effects are dose related.[43]

Exenatide is available in 5- and 10-μg fixed-dose pen devices.[35,36] Patients typically start treatment with a dosage of 5 μg twice daily, administered before meals. Patients may take their doses before lunch and before the evening meal if they do not eat breakfast. The dosage may then be titrated to 10 μg twice daily as indicated and tolerated. Exenatide should be administered from 60 minutes to immediately before meals—with less nausea reported when given closer to the meal, but with maximum satiety when given 1 hour before the meal. The 2 daily doses should be at least 6 hours apart.

Exenatide extended release, which was approved for use by the Food and Drug Administration in January 2012, is administered once weekly.[36] It is available in single-dose trays, with each tray providing an injection of 2 mg exenatide. Thus, patients receive 4 trays per month. Patients may administer injections at any time, without regard to mealtime. Because of its very long half life,
initial glucose lowering may take longer in the formulation.

Patients should read the directions carefully before administering extended release exenatide. A step-by-step set of directions is provided with this medication. Patients should be counseled to tap the powder in the exenatide extended release tray to loosen it, if necessary, and to use the orange connector to connect the vial to the syringe. Diluent should be injected into the vial, which should be shaken until the drug is fully suspended. Patients or caregivers should then withdraw the suspension into the syringe, attach the 23-gauge, 5/16-inch needle, and push the plunger until the top is even with the dotted line on the syringe. The dose may be injected subcutaneously into the stomach, back of the arm, or thigh. Approximately 77% of people feel a bump after injection under the skin, and about 1 in 5 individuals may have a localized reaction from the injection. However, only approximately 1% of patients discontinued exenatide extended release because of injection site reactions.

Exenatide twice daily primarily affects postprandial glucose levels. The longer-acting agents (liraglutide and exenatide extended release) reduce both FPG levels and postprandial glucose levels and, therefore, result in greater lowering of glucose levels.

Risks of hypoglycemia with the use of GLP-1 receptor agonists are low, because these agents work only in the presence of hyperglycemia. However, when GLP-1 receptor agonists are added to existing sulfonylurea therapy, the risks of sulfonylurea-induced hypoglycemia may be increased, and downward dose adjustment or discontinuation of the sulfonylurea may be warranted.

Because the most common adverse effects of GLP-1 receptor agonists are gastrointestinal in nature (eg, nausea, vomiting) and are dose-related, patients should not be “force titrated.” Rather, doses should be gradually escalated as the patient tolerates each dose level (up to 1.8 mg daily maximum for liraglutide and 10 mcg twice daily maximum for exenatide short-acting). The only dose level for exenatide once weekly is 2 mg, which, because of the long half-life of this agent, takes some time to reach a steady state. Nausea is less common with longer-acting agents and dissipates in almost all patients by 12 weeks. Because these drugs affect gastric emptying, patients should be counseled to eat very slowly so as not to have feelings of bloating. These agents should not be used in people with diabetic gastroparesis, a form of diabetic neuropathy.

If a dose of liraglutide is missed and less than 12 hours have passed from when the patient should have taken it, the dose should be taken as soon as possible. If a dose of liraglutide is missed and more than 12 hours have passed from when it should have been taken, the patient should skip the missed dose and resume the usual dosing schedule with the next scheduled dose. The patient should not double the dose to “catch up.” If a patient misses a dose of exenatide extended release, the dose should be taken as soon as remembered, provided that the next scheduled dose is at least 3 days from the current time. However, if a dose of exenatide extended release is
missed and the next scheduled dose is less than 3 days from the current time, the patient should wait until the next regularly scheduled dose to restart the medication.44

Are there oral forms of GLP-1 receptor agonists?

Many patients are aware that several new drugs are available to manage the hyperglycemia of T2DM. Represented prominently in the AACE treatment algorithm6 are DPP-4 inhibitors, primarily because of their good tolerability and low risk of hypoglycemia. However, important differences exist between that class of incretin-based medications and GLP-1 receptor agonists. The DPP-4 inhibitors work to inhibit the enzyme that degrades GLP-1. Although DPP-4 inhibitors may inhibit the degradation of GLP-1, many patients with T2DM have an impaired incretin effect, so ambient GLP-1 levels may already be compromised in these individuals.49 This compromised condition may partly explain the difference in glucose-lowering potential between DPP-4 inhibitors and GLP-1 receptor agonists, in favor of GLP-1 receptor agonists,79,50,51 which directly provide GLP-1 agonism at pharmacologic or supraphysiologic levels.52 The DPP-4 inhibitors primarily affect postprandial glucose levels.53

The differences in effects on GLP-1 levels may partly explain the differences in weight effects between GLP-1 receptor agonists and DPP-4 inhibitors.29,33 Recent data suggest that a reduced incretin effect and fasting hyperglucagonemia may constitute early steps in the pathophysiologic development of T2DM, detectable even in obese people who, despite their insulin-resistant state, have normal glucose tolerance.54

References


