Physicians have many options available for treating patients with type 2 diabetes mellitus (T2DM). Making decisions on types of pharmaceuticals to use and when to introduce them into the treatment regimen can be a complex process. In addition, nutrition and exercise must be considered in any comprehensive treatment plan. The author describes the case of an African American woman with uncontrolled T2DM, obesity, hyperlipidemia, low bone mass, menopausal symptoms, stage 3 chronic kidney disease, distal sensory neuropathy, and background retinopathy. An aggressive, comprehensive treatment plan developed for this patient included pharmaceuticals (triple oral therapy: metformin, pioglitazone hydrochloride, and sitagliptin phosphate), nutrition counseling (with a registered, licensed dietitian), and exercise. Treatment led to substantial improvements in the patient’s daytime glucose level, glycosylated hemoglobin level, and body weight at 3-month follow-up. Further interventions were needed to address the patient’s hyperlipidemia and low bone mass. The author offers physician guidelines for making decisions on glycemic control for patients with T2DM and for managing hyperlipidemia. He also strongly recommends incorporating nutrition counseling by registered, licensed dietitians and exercise (preferably of a weight-bearing nature) into treatment plans for patients with T2DM, hyperlipidemia, and low bone mass.

This supplement is supported by an educational grant from Merck & Co, Inc, to the American College of Osteopathic Family Physicians.
aggressive combination pharmaceutical therapy: metformin (titrated up to 1000 mg twice daily) with pioglitazone hydrochloride (titrated up to 45 mg/d). With this treatment regimen, the patient’s HbA1c level decreased to 7.0% at 3 years previous to her initial visit and was maintained at 7.2% at 6 months prior to her initial visit.

Marian reported having menopausal symptoms for approximately the previous 5 months. She also admitted to having little physical activity and noted that she had some recent weight gain. In addition, she said she was a nonsmoker with a family history of cardiovascular disease (CVD). Medical records indicated that her fasting plasma glucose (FPG) was at a reasonable level, 100 mg/dL to 120 mg/dL, though her daytime glucose levels were greatly elevated—between 180 and 210 mg/dL.

In addition to using metformin and pioglitazone to manage her T2DM, Marian was taking the following medications: a lipid-lowering agent (atorvastatin calcium, 20 mg/d); an angiotensin-converting enzyme (ACE) inhibitor (lisinopril, 20 mg twice daily); hydrochlorothiazide (25 mg/d); and an antiplatelet agent (aspirin; 81 mg/d).

Marian’s pertinent physical examination and laboratory findings at her initial visit are reported in Table 1. Her height was 5 ft 5 in, and her weight was 193 lb, with a waist circumference of 38 in and a body mass index (BMI) of 31.2. Her blood pressure was controlled, at 128/78 mm Hg, and her heart rate was 76 beats per minute. The examination also revealed that Marian had mild background retinopathy and loss of distal vibratory perception (based on placement of a 128 Hz tuning fork on toe).

Initial laboratory test results (Table 1) revealed that Marian’s FPG level had increased to 130 mg/dL, and her HbA1c level had increased to 7.6%. Her thyroid-stimulating hormone level (1.2 mIU/L) indicated normal thyroid function. Her glomerular filtration rate (GFR) indicated abnormal renal function, at 55 mL/min/1.73 m² (Table 1). This GFR was calculated using the abbreviated Modification of Diet in Renal Disease (abbreviated MDRD) system. In her comprehensive metabolic panel results, Marian’s blood urea nitrogen was somewhat elevated, at 29 mg/dL, and the creatinine level was 1.1 mg/dL—suggestive of renal problems when considered with the GFR. Liver function test results and calcium and phosphorus levels were normal. Lipid test results indicated that Marian had mixed hyperlipidemia (Table 1). Dual-energy x-ray absorptiometry (DXA) results showed a bone mineral density T-score of –3.0 indicative of osteoporosis.

**Clinical Considerations**

The following clinical issues were deduced from Marian’s medical history, physical examination findings, and laboratory test results. She had uncontrolled T2DM and obesity with hyperlipidemia, though her blood pressure appeared to be controlled. She had distal sensory neuropathy and background retinopathy, as well as stage 3 chronic kidney disease. She was menopausal and had low bone mass.

Marian was currently taking two oral agents, but her T2DM remained uncontrolled. How should her therapy be advanced? Many options were available, including sulfonylureas, meglitinides, AGIs, DPP-IV inhibitors, incretin mimetics, and basal insulin. The strategy for making such therapeutic decisions is based on data showing that oral agents and exenatide lower HbA1c levels by approximately 1% to 1.5%. When medications are combined, an additional 1% reduction in HbA1c levels is usually achieved for each additional agent. Insulin has an unlimited capacity to lower HbA1c levels.

In light of these considerations, how is the physician to decide when to add a new oral antidiabetes agent to a patient’s treatment regimen or when to advance to insulin therapy? The basic rationale for making such a decision can be described as follows. If the addition of a given medication can be expected to reduce the patient’s HbA1c level by 1%—and if this 1% reduction reaches the treatment goal for that patient—then that medication should be used. However, if the expected 1% HbA1c reduction from a given medication is not enough to reach the treatment goal for that patient, then the medication should not be used. In that case, insulin therapy should be started.

The Texas Diabetes Council (TDC) Diabetes Tool Kit, which is posted on the Texas Department of Health Services Web site, includes an algorithm (Appendix) that can be used for making decisions on glycemic control.

---

**Table 1**

<table>
<thead>
<tr>
<th>Component</th>
<th>Value</th>
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<tr>
<td><strong>Examination Findings</strong></td>
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<tr>
<td>Height, in</td>
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<tr>
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<tr>
<td>Body mass index</td>
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<tr>
<td>Blood pressure, mm Hg</td>
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<tr>
<td><strong>Laboratory Findings</strong></td>
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<tr>
<td>Fasting plasma glucose, mg/dL</td>
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<tr>
<td>Glycosylated hemoglobin, %</td>
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<td>Thyroid-stimulating hormone</td>
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<tr>
<td>Comprehensive metabolic panel</td>
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<td>— albumin, g/dL</td>
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<tr>
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<td>— LDL-C</td>
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<td>— HDL-C</td>
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<td>— triglycerides</td>
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<td>DXA T Score</td>
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<tr>
<td>Abnormal Examination Findings</td>
<td></td>
</tr>
<tr>
<td>— Mild background retinopathy</td>
<td></td>
</tr>
<tr>
<td>— Loss of distal vibratory perception</td>
<td></td>
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</tbody>
</table>

Abbreviations: DXA, Dual-energy x-ray absorptiometry test for bone mineral density; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
for patients with T2DM. This decision algorithm, which we use at the Texas Diabetes Council, is more aggressive than that presented by Nathan et al. Our goal is to achieve an HbA1c level of less than or equal to 6%—provided that this level can be achieved without hypoglycemia. We want the fasting self-monitored blood glucose level to be less than or equal to 100 mg/dL, and the 2-hour postprandial self-monitored blood glucose level to be less than or equal to 140 mg/dL. In addition, medical nutrition counseling and an exercise program may be incorporated into the patient’s treatment plan as part of the initial intervention.

Initial pharmaceutical intervention, as presented in the TDC algorithm, consists of dual therapy if HbA1c levels are greater than or equal to 7.5%. (Monotherapy may be considered when a patient has an HbA1c level less than 7.55.) Dual therapy options include various combinations of metformin, meglitinide, sulfonylureas, AGIs, DPP-IV inhibitors, TZDs, exenatide (an incretin mimetic), and insulin. If at the 3-month follow-up the patient’s HbA1c level is less than 1% above goal, a third oral antidiabetes agent or exenatide is added to the treatment regimen. If at the 3-month follow-up that patient’s HbA1c level is greater than 1% above goal, insulin is added as a third agent.

Development of Treatment Plan for Patient in Current Case

Marian continued taking metformin and pioglitazone. To help reduce the patient’s HbA1c level of 7.6%, exenatide (5 μg twice daily) was added as a third pharmaceutical agent. Although most patients respond to exenatide with the typical 1%-to-1.5% decrease in HbA1c levels, a small subset of patients with very poor glycemic control has been shown to have HbA1c reductions as great as 3% to 5% when starting exenatide. Exenatide has additional potential benefits of weight loss and improvement in β-cell function, as well as no increased risk of hypoglycemia when used in combination with metformin or TZDs.

Unfortunately, Marian stopped using exenatide after 4 weeks because of gastrointestinal adverse effects (ie, vomiting). Although our experience has shown that such adverse effects are temporary in many patients using exenatide, Marian decided that the adverse effects of the medication were not worth the potential benefits. Thus, an alternative third medication needed to be found to achieve glycemic control.

Marian had an HbA1c level of 7.6%. After her pharmaceutical options were explained to her, she decided to try a third regimen of metformin, pioglitazone, and sitagliptin phosphate (a DPP-IV inhibitor). She declined insulin therapy and intended to augment the triple oral regimen with a dedicated diet, exercise, and weight loss program in order to reach the HbA1c goal of less than or equal to 6%. The efficacy of adding a DPP-IV inhibitor is well documented. Rosenstock et al reported a significant decrease of 0.7% in HbA1c levels with the use of sitagliptin phosphate (100 mg/d) and pioglitazone hydrochloride (30 mg/d to 45 mg/d), compared with placebo plus pioglitazone, in patients with T2DM. Goldstein et al reported a 2% reduction in HbA1c levels when sitagliptin phosphate (50 mg twice daily) plus metformin (1000 mg twice daily) were used, versus placebo.

Note that these effects of adding an agent or starting dual therapy are consistent with previously discussed rules regarding the effects of combining antidiabetic agents. We do not have data on triple oral therapy with sitagliptin plus metformin plus a TZD. However, experience in our clinics supports an additional reduction in HbA1c levels of 0.5% to 1% with a third agent.

Although sitagliptin was used as the third medication in Marian’s treatment to achieve glycemic control, other medication options would have also been potentially useful. Garber et al found that vildagliptin (another DPP-IV inhibitor) produced an additive effect on HbA1c levels in patients with T2DM when used at a dosage of 100 mg daily and when administered with pioglitazone (45 mg/d). Thus, the additive benefits of using a DPP-IV inhibitor with a TZD agent are not unique to only one of the DPP-IV inhibitors.

Still other medication combinations might have been effective in reaching our goal. Ahren et al reported that the use of vildagliptin (50 mg/d) with metformin (1500 mg/d to 3000 mg/d) had an additive effect in decreasing HbA1c levels by 1.1% (±0.2%) in patients with T2DM, compared with placebo and metformin (P<.001). Nauck et al reported that the use of either sitagliptin plus metformin or glipizide plus metformin resulted in reductions in HbA1c levels, but sitagliptin plus metformin had the added benefit of weight loss of approximately 5 lb.

**Diet and Exercise**

To manage her T2DM effectively, Marian required comprehensive diet and exercise plans in addition to aggressive pharmaceutical treatment. Thus, she was referred to a registered, licensed dietitian for assessment, goal-setting, and meal planning, and she began regular low-intensity exercise.

Proper medical nutrition therapy entails referral to a registered, licensed dietitian, who will initiate a program for the patient addressing a number of vital areas (Figure). The nutrition program created by a registered, licensed dietitian typically includes assessment of the patient’s anthropometrics (ie, measurements of size, weight, and proportions of the body), lifestyle, and medical records (including glucose history). In addition, a psychological evaluation may be used by the dietitian to assess the patient’s readiness and ability to change personal behaviors that may be contributing factors to T2DM.

After assessment of the patient, the dietitian establishes goals and timetables for reductions in the patient’s weight (of at least 5%), glucose level, lipid level, and blood pressure. Finally, the dietitian assists the patient in meal planning. A dietitian is an invaluable part of optimizing therapy for a patient with T2DM.

A patient’s nutrition program should be augmented with an exercise program. However, how is a physician to determine the level of activity most suitable for a particular patient—and if a cardiac exercise stress test needs to be performed? The algorithm used at the Texas Diabetes Council, provides a pathway for making decisions regarding this matter.

If the patient has T2DM or impaired
Medical Nutrition Therapy

- Referral to Registered, Licensed Dietitian
- Assessment
  - Anthropometrics
  - Lifestyle
  - Medical history
  - Psychological evaluation
  - Glucose monitoring
- Goal Establishment
  - Weight reduction, ≥5%
  - Glucose levels
  - Lipid levels
  - Blood pressure
- Meal Planning

Figure. Medical nutrition therapy provided by registered, licensed dietitians for patients with type 2 diabetes mellitus.

Fasting glucose levels or both—and there is evidence of CVD—a stress test should be done. If the patient has T2DM and proliferative retinopathy or peripheral neuropathy, low-intensity exercise should be prescribed. Low-intensity exercise should also be prescribed if the patient has T2DM and at least one of the following risk factors: hypertension, hyperlipidemia, smoking, family history of CVD. Marian was started on a therapy program of low-intensity exercise because she had distal sensory neuropathy.

Patients who have T2DM but no additional risk factors or symptoms may begin a program of vigorous exercise if they are younger than 35 years. If they are 35 years of age or older, they may begin a program of moderate exercise.4(p3.1) For any patient with T2DM, a stress test should be done before advancing the patient to a higher level of activity.4(p3.1)

Current Case Follow-Up

After 1 month of triple oral therapy, nutrition counseling, and low-intensity exercise, Marian had results as reported in Table 2. Although her FPG level was virtually unchanged (125 mg/dL), her daytime glucose level dropped substantially, from 180-210 mg/dL to an average of 155 mg/dL. Her HbA1c level showed a mild reduction, from 7.6% to 7.2%. Marian’s weight also showed a mild improvement—from 193 lb to 188 lb. Her blood pressure, at 130/76 mm Hg, was in an acceptable range. Her lipid profile was essentially unchanged from baseline. The patient reported no adverse effects after 1 month.

After 3 months of treatment (Table 2), Marian’s FPG level (120 mg/dL) was still not at goal, but it was slightly reduced from the 1-month level. Her daytime glucose level continued to show improvement, reduced to an average of 145 mg/dL. This level falls within the recommended guidelines of the American Diabetes Association (<140-180 mg/dL),13 though not quite within the guidelines of the American Association of Clinical Endocrinologists (<140 mg/dL).14 Marian’s HbA1c level also continued its decrease, to 6.7%, as did her weight, to 179 lb.

Marian’s 3-month lipid profile showed little sign of improvement (Table 1). However, in the setting of diabetes mellitus, it should be noted that it is important to achieve glucose goals first—before trying to manage lipid abnormalities with pharmaceuticals. Correcting secondary causes of hyperlipidemia—such as hyperglycemia, alcohol use, or hypothyroidism—is absolutely necessary before starting additional drug therapy.

Marian’s glucose, HbA1c, and weight were all at encouraging levels at 3-month follow-up (Table 1), with no adverse effects. Thus, it was deemed desirable to begin intervention for hyperlipidemia.

Hyperlipidemia

Various medications are available for managing hyperlipidemia, including atorvastatin, fluvastatin sodium, lovastatin, pravastatin sodium, rosuvastatin calcium, simvastatin, ezetimibe, fibrates, and niacin.15-24 Any of these medications may be effective in treatment, but how is a physician to choose the most effective medication for any particular patient? As first described by Jones et al,15 a lipid-lowering hydroxymethylglutaryl-coenzyme A reductase inhibitor (statin) can be selected based on the desired percent reduction in low-density lipoprotein cholesterol (LDL-C). Reference to the TDC table4(p6.4) can help a physician narrow the available choices for selecting a lipid-lowering agent. For example, if a 25% reduction in LDL-C is desired, either fluvastatin, lovastatin, or pravastatin would be a wise choice. However, if a 50% reduction in LDL-C is needed, atorvastatin, rosuvastatin, or simvastatin would be a better choice.4(p6.4)

The addition of ezetimibe to the use of a statin has been shown to reduce LDL-C levels an additional 12% to 18%.25-27 This finding is clinically important, because adverse effects from the use of statins are dose dependent. Thus, the use of ezetimibe can result in several effective doublings of a statin dose—without causing the adverse effects associated with statins.25-27

Basic guidelines in hyperlipidemia management for patients with T2DM, as followed by the Texas Diabetes Council, can be summarized as follows:

- When a patient has a lipid abnormality, the secondary causes of hyperlipidemia should be addressed before initiating lipid-lowering pharmacotherapy.
- When a patient has elevated LDL-C levels (>100 mg/dL), a statin should be used in treatment, with the addition of ezetimibe if lipid goals are not reached.
- When a patient has isolated low levels of high-density lipoprotein cholesterol (HDL-C<40 mg/dL), optimize lifestyle changes (ie, diet, exercise, smoking cessation) and start fibrate, niacin, fish oil, or a statin.
- When a patient has triglyceride concentrations in the range between 150 and 199 mg/dL, optimize lifestyle changes. When triglyceride concentrations are in the range between 200 and 399 mg/dL, optimize lifestyle changes and start fibrate, niacin, and/or fish oil. When triglyceride concentrations are 400 mg/dL or greater, optimize lifestyle changes and start fibrate, niacin, and/or fish oil and (if LDL-C not at goal) a statin.
Other Considerations Requiring Referral

For some patients with T2DM, other clinical considerations may arise during treatment. Such considerations may include the need for referral to an ophthalmologist or a nephrologist for additional management of microvascular disease or the need for further management of bone loss.

Any patient with T2DM in which the creatinine level reaches 2 to 2.5 mg/dL would be a good candidate for referral to a nephrologist. Referral should be made before creatinine reaches higher levels than these—that is, before kidney dialysis may become necessary. In the current case, the patient’s creatinine level was only 1.1 mg/dL. Thus, intervention by a nephrologist was not necessary.

Patients with T2DM should be referred to an ophthalmologist when ocular regions are found to be affected by microvascular disease. In the current case, the patient was known to have retinopathy. Thus, she needed to see an ophthalmologist.

Marian received tight, aggressive treatment for T2DM, with lipid-lowering medications, blood pressure medications, and triple oral therapy for hyperglycemia, as well as nutrition counseling and an exercise plan. This type of treatment can help prevent macrovascular events and stabilize or reverse microvascular events. As Jeffrey S. Freeman, DO, reports beginning on page 55 in this supplement issue of *JAOA—The Journal of the American Osteopathic Association*, tight control of glucose and blood pressure in patients with T2DM can result in substantial improvements in such parameters as 24-hour urine GFR and macroalbuminuria levels.

**Bone Disease—Medications Versus Weight-Bearing Exercise**

The DXA results for Marian revealed a pathologic bone mineral density T-score of −3.0. There were a number of options to consider regarding management of her low bone mass. Two options were to measure her levels of intact parathyroid hormone (PTH) and 25-hydroxy (25-OH) vitamin D. This patient had stage 3 chronic kidney disease, with a GFR of 55 mL/min/1.73 m². Because this is early stage 3 chronic kidney disease, one might decide against PTH testing. Calcium and phosphate levels are usually normal in patients with stages 1 to 3 chronic kidney disease. However, some physicians recommend measuring PTH, calcium, and phosphorus levels every 12 months in patients with stage 3 chronic kidney disease.

In this particular case, we decided not to evaluate the patient for secondary hyperparathyroidism at this time. Rather, we decided to reevaluate her renal function after optimizing her diabetes management. If there was improvement in 3 months, testing might not be needed. If Marian’s renal status did not improve, then levels of PTH and 25-OH vitamin D would be measured.

Many physicians would likely opt for beginning treatment with a bisphosphonate to manage this patient’s bone loss. Other physicians would probably begin estrogen (hormone-replacement) therapy with this patient. However, there is another option for increasing bone density—weight-bearing exercise.

Weight-bearing exercise yields increases in bone density comparable to increases that can be achieved with medications. A meta-analysis of resistance training in premenopausal women showed variable results of 1% to 3.9% increases in the women’s bone density. These results are similar to results achieved with the use of estrogen, bisphosphonates, or teraparatide. Thus, weight-bearing exercise should be considered as part of an aggressive, comprehensive treatment plan for patients with diabetes mellitus and bone loss.

**Comment**

The current case involved a menopausal women with uncontrolled T2DM, hyperlipidemia, and low bone mass. Aggressive treatment with triple oral therapy (metformin, pioglitazone, and sitagliptin), as well as nutrition counseling and exercise, led to substantial improvement in her daytime glucose, HbA₁c levels, and body weight at the 3-month follow-up.

The effects of each oral antidiabetes agent are additive. To help reduce a patient’s HbA₁c level, exenatide can be added as a third pharmaceutical agent, though it may result in gastrointestinal adverse effects. If a patient’s HbA₁c level is less than 8%, a DPP-IV inhibitor may be a preferable third option for achieving glycemic control.

Further interventions were necessary to address Marian’s hyperlipidemia and low bone mass. For hyperlipidemia, a statin can be selected based on the desired percent reduction in LDL-C. The addition of ezetimibe to the use of a statin can result in several effective doublings of a statin dose—without causing the adverse effects associated with statins.

**Table 2**

<table>
<thead>
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<th>Follow-up Findings</th>
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<tr>
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<tr>
<td><strong>3 Months</strong></td>
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<td>— triglycerides</td>
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<tr>
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<td>— no reported abnormal examination findings</td>
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**Abbreviations:** HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
Medical nutrition counseling by a licensed, registered dietitian and an exercise program are crucial in a comprehensive treatment plan for a patient with T2DM, hyperlipidemia, and low bone mass. Weight-bearing exercises, in particular, can achieve substantial improvements in bone mineral density.

Aggressive, comprehensive treatment for patients with T2DM, hyperlipidemia, and low bone mass can help prevent macrovascular events and stabilize or reverse microvascular events.

References

Appendix

(Reprinted with permission of the Texas Diabetes Council.)

Glycemic Control Algorithm For Type 2 Diabetes Mellitus In Children And Adults

**Goals**

1. Diabetes Education and
2. SMBG and
3. Medical Nutrition, Weight Control, Exercise and
4. Dual Therapy or Consider Monotherapy if A1C < 6.5%

---

**Initial Intervention**

- Add additional oral agent or exenatide if A1C less than 1% above goal
- Otherwise add Insulin as third agent (see Insulin Algorithm)

**Goals not met after 3 months**

Add insulin (see Insulin Algorithm)
Consider referral to endocrinologist

---

**Abbreviations**

- AGI: Alpha-Glucosidase Inhibitors
- CAD: Coronary Artery Disease
- DPP-4: Dipeptidyl peptidase-4 Inhibitor
- IHD: Ischemic Heart Disease
- PP: Postprandial
- SMBG: Self-monitored Blood Glucose
- SU: Sulfonylureas
- T2D: Thiazolidinedione

---

**Footnotes:**

1. Goals must be individualized. A1C ≤ 6% is the goal if possible without significant hypoglycemia. Less stringent treatment goals may be appropriate for patients with a history of severe hypoglycemia, patients with limited life expectancies, very young children and individuals with comorbid conditions. A1C is referenced to a non-diabetic range of 4-6% using a DCCT-based assay. ADA Clinical Practice Recommendations. Diabetes Care 2007;30(supp1):S9-10
2. If initial presentation is hyperglycemia PLUS weight loss, use insulin, with or without oral agents, as the initial intervention (see Insulin Algorithm). Other agents may be introduced as glycemic control improves.
3. These interventions should be maintained long-term (see Medical Nutrition, Weight Loss, and Exercise Algorithms).
4. Consider stopping/reducing dose of SU as a component of therapy due to risk of hypoglycemia as A1C approaches goal.
5. Metformin is the only FDA-approved oral antidiabetic agent in children (> age 10); other agents may be used at the discretion of the clinician.
6. If a SU is selected, low dose glipizide ER or glimepiride are recommended because they have a lower incidence of hypoglycemia than glyburide.
7. DPP-4 inhibitor should not be used in combination with Exenatide.

---

**Options for Dual/Combination Therapy**

- Metformin + TZD
- Metformin or TZD + DPP-4 or SU or Meglitinide
- Metformin + TZD or SU + Exenatide or DPP-4 or AGI
- Metformin + TZD, AGI or SU + Insulin

*SU is not recommended if A1C < 6.5%
GLYCEMIC CONTROL BIBLIOGRAPHY

**Recent Review Articles**

**Metformin or Sulfonylurea + Acarbose**

**Metformin + Thiazolidinedione**
Pioglitazone:
Rosiglitazone:

**Sulfonylurea + Thiazolidinedione**
Pioglitazone:
Rosiglitazone:

**Metformin or Sulfonylurea + Exenatide**

**Nateglinide or Repaglinide + Metformin**

**Repaglinide:**

**Nateglinide:**

**Nateglinide or Repaglinide + Thiazolidinedione**
Nateglinide:
Repaglinide:

**Triple Therapy**
Sulfonylurea + Metformin + Alpha glucosidase inhibitors:

Sulfonylurea + Metformin + Thiazolidinedione:

Sulfonylurea + Metformin + Exenatide: