Type 2 diabetes mellitus (T2DM) is a disease of special concern in regard to the Hispanic population in the United States. There are several reasons for this heightened concern. Hispanic people make up the largest ethnic minority group in the United States, comprising almost 40 million individuals, or approximately 13% of the total US population. Among Hispanic populations, Mexican Americans—concentrated most heavily in the American Southwest—make up the largest ethnicity. Mexican Americans are about 1.7 times more likely to have T2DM than are non-Hispanic white persons. Other Hispanic ethnicities—such as Cubans and Puerto Ricans—have different gene...
pools than Mexican Americans, each with its own compilation of potential healthcare issues. Some of these gene pools include high risk factors for T2DM, others do not.

A number of studies have indicated that the incidence of impaired glucose tolerance and metabolic syndrome is greater in the Hispanic population than in the non-Hispanic white population of the United States.2-6

Using data from the Third National Health and Nutrition Examination Survey (NHANES III) and prior Health and Nutrition Examination Surveys, Harris et al4 reported on a subsample of 6587 adults (aged ≥20 years) for whom fasting plasma glucose values were obtained and a subsample of 2844 adults (aged 40-74 years) who underwent an oral glucose tolerance test. The subjects were analyzed as three ethnic groups: non-Hispanic white persons, Mexican American, and African Americans. The researchers found that greater percentages of Mexican Americans than other ethnic groups had impaired fasting glucose and impaired glucose tolerance—risk factors for T2DM and metabolic syndrome.4

Meigs et al5 compared the rates of metabolic syndrome among 3224 white subjects in the Framingham Offspring Study and 1081 non-Hispanic white subjects and 1656 Mexican American subjects in the San Antonio Heart Study. The comparison was based on the definition of metabolic syndrome (ie, associated with waist circumference) described in the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.7 This analysis revealed that metabolic syndrome was more prevalent among Mexican Americans—both men and women—than among subjects in the other groups that Meigs et al examined.5

Ford et al6 also concluded that the incidence of metabolic syndrome and insulin resistance is higher among Mexican Americans than among other ethnic groups in the United States. It should be noted that this conclusion does not necessarily mean that such individuals currently have T2DM, though it does mean that they probably have obesity and are at risk for T2DM as a result of insulin resistance.

According to projections by the American Diabetes Association (ADA), the number of non-Hispanic white people with diagnosed diabetes mellitus in the United States is likely to increase by 27% by 2020, and the number of non-Hispanic African Americans by 50%.3 By contrast, the number of US Hispanic people with diagnosed diabetes mellitus is projected to increase by 107% by 2020.3 Hence, Hispanic persons with T2DM represent an increasing healthcare “burden” for the United States in terms of both healthcare costs and physician challenges.

The present article describes the case of a Hispanic man, 62 years of age, with T2DM. The T2DM was newly diagnosed, rather than of recent onset. The article also discusses various T2DM complications and the intervention options that are available to address these complications, with particular emphasis on the Hispanic population.

Figure 1. Geographic distribution of the Hispanic population in the United States, including estimated populations of selected ethnic groups in Arizona, California, Florida, Illinois, New Jersey, New York, Pennsylvania, and Texas. Adapted from United States Census 2000, US Census Bureau.1
Case Presentation

The patient in the current case, Julio (not his real name), worked as a clerk in a convenience store. He reported having increasing fatigue and intermittent blurred vision for approximately 1.5 years before his initial visit. He also reported tingling and decreased sensation in both his feet and noted that superficial wounds to his body healed more slowly than in the past. Julio was obese and a smoker. He said he recently began smoking again after having quit the habit 10 years previously. He also said that he was currently taking no medications.

The results of Julio’s physical examination and laboratory tests at his initial visit are shown in the Table. His height was 5 ft, and his weight was 212 lb. He was extremely obese, with a body mass index (BMI) of 41.4. His blood pressure was indicative of hypertension, at 144/86 mm Hg, and his heart rate was 88 beats per minute (the upper range of “normal”).

An eye examination of Julio revealed one or two microaneurysms during his initial visit. Peripheral vascular disease (PVD) was implied by absent dorsalis pedis and absent posterior tibial pulses. Also noted were absent ankle reflexes, absent plantar sensation to standard (10 g) monofilament testing, and reduced distal vibratory perception (based on placement of a 128-Hz tuning fork on toe).

Results of Julio’s laboratory tests (Table) suggested several abnormalities, including a fasting plasma glucose level of 169 mg/dL and a 2-hour postprandial random plasma glucose level of 280 mg/dL. Julio’s glycated hemoglobin (HbA1c) level was 7.8%. His total cholesterol level was 228 mg/dL, with a low-density lipoprotein cholesterol (LDL-C) level of 146 mg/dL and a high-density lipoprotein cholesterol (HDL-C) level of 32 mg/dL. Julio’s triglyceride concentration was 250 mg/dL, his blood urea nitrogen level was 35 mg/dL, and his creatinine level was 1.7 mg/dL.

Julio’s high-sensitivity C-reactive protein (hs-CRP) level was 3.2 mg/L, which is higher than normal. The test for urine microalbumin found 120 μg creatinine—indicative of macroalbuminuria—while the 24-hour urine study found a creatinine clearance rate of 46 mL/min and an albumin shedding rate of 1.15 g/24 h.

The results of Julio’s physical examination and laboratory tests led to the diagnosis of a number of health problems. He had newly diagnosed T2DM (rather than T2DM of recent onset), as well as diabetic peripheral neuropathy, background retinopathy, and diabetic nephropathy with macroalbuminuria. In addition, there was evidence of hypertension, PVD, and mixed dyslipidemia.

Julio had not previously had diabetes mellitus diagnosed, though it was clear that he had T2DM, microvascular abnormalities, and macrovascular abnormalities for several years. He urgently needed pharmacologic treatment and other forms of therapy to manage his condition. Unfortunately, this patient is representative of many other individuals with T2DM, who, for unknown reasons—perhaps related to high medical

### Table

<table>
<thead>
<tr>
<th>Examination and Laboratory Test Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Component</td>
</tr>
<tr>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Vital Signs</td>
</tr>
<tr>
<td>□ Height, in</td>
</tr>
<tr>
<td>□ Weight, lb</td>
</tr>
<tr>
<td>□ Body mass index</td>
</tr>
<tr>
<td>□ Blood pressure, mm Hg</td>
</tr>
<tr>
<td>Laboratory Results</td>
</tr>
<tr>
<td>□ Fasting plasma glucose, mg/dL</td>
</tr>
<tr>
<td>□ Glycosylated hemoglobin, %</td>
</tr>
<tr>
<td>□ Thyroid-stimulating hormone, mIU/L</td>
</tr>
<tr>
<td>□ Creatinine clearance rate, mL/min</td>
</tr>
<tr>
<td>□ Albumin shedding rate, mg/24 h</td>
</tr>
<tr>
<td>□ Urine microalbumin, μg creatinine</td>
</tr>
<tr>
<td>□ hs-CRP, mg/L</td>
</tr>
<tr>
<td>Comprehensive Metabolic Panel, mg/dL</td>
</tr>
<tr>
<td>□ Blood urea nitrogen</td>
</tr>
<tr>
<td>□ Creatinine</td>
</tr>
<tr>
<td>Lipid Profile, mg/dL</td>
</tr>
<tr>
<td>□ Total cholesterol</td>
</tr>
<tr>
<td>□ LDL-C</td>
</tr>
<tr>
<td>□ HDL-C</td>
</tr>
<tr>
<td>□ Triglycerides</td>
</tr>
<tr>
<td>Adverse Events</td>
</tr>
<tr>
<td>□ Central obesity</td>
</tr>
<tr>
<td>□ Absent dorsalis pedis</td>
</tr>
<tr>
<td>□ Absent posterior tibial pulses</td>
</tr>
<tr>
<td>□ Absent ankle reflexes</td>
</tr>
<tr>
<td>□ Absent plantar sensation</td>
</tr>
<tr>
<td>□ Reduced distal vibratory perception</td>
</tr>
</tbody>
</table>

* Findings at 9-month follow-up included ability to walk 1 mile without claudication; no painful neuropathy; stable retinopathy; reduced fruit intake; no longer snacking on peanuts; weight reduction of 12 lb; and enthusiasm about exercise.

Abbreviations: HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol.
Figure 2. Initial treatment plan, with subsequent additions, used for the patient. *Irbesartan was titrated to 300 mg/d. †Clopidogrel was used as a replacement for aspirin because of patient’s gastrointestinal intolerance. ‡Added at 3-month follow-up.

Development of Treatment Plan

Monotherapy with a glucose-lowering agent was indicated in the current case. Such agents can include metformin; dipeptidyl peptidase IV (DPP-IV) inhibitors (eg, sitagliptin phosphate); incretin mimetics (eg, exenatide); sulfonylureas (eg, glipizide); and thiazolidinediones (TZDs, such as pioglitazone hydrochloride).8,9

The process of agent selection involves a stepwise approach, as suggested by the ADA and the European Association for the Study of Diabetes.8,9 The goal of the ADA guidelines is to reduce the patient’s HbA1c level to less than 7% (or as close to normal [<6%] as possible without causing hypoglycemia).8

The therapeutic algorithm for management of T2DM published by Nathan et al8 involves initial monotherapy with metformin. If the HbA1c level remains above 7% after 3 months, then basal insulin, glitazone, or a sulfonylurea would be the next choice for treatment. However, this algorithm may be too limiting in some cases.

To select the most appropriate medication for the current patient, it was necessary to determine exactly where he was in terms of the progression of his T2DM. Julio had insulin resistance with a substantial reduction in insulin secretion. Because he had T2DM several years before diagnosis, he may have also had a 50% reduction in his β-cell function by the time of his initial visit.10 Thus, pharmacologic treatment needed to be directed toward this progressive loss of β-cell function.

The results of NHANES III11 provided evidence that the duration of a patient’s T2DM influences the type of treatment being used by that patient. There were 1480 subjects with T2DM in NHANES III,11 including 590 non-Hispanic white subjects, 405 non-Hispanic African Americans, 450 Mexican Americans, and 35 individuals of other ethnicities. Mexican Americans in the survey who had T2DM that was diagnosed less than 5 years earlier were most likely to be using oral antidiabetes agents or exclusively diet therapy. Only about 10% of the Mexican American patients at that early stage of T2DM were using insulin. Mexican Americans who had T2DM that was diagnosed between 5 and 14 years earlier were much less likely to rely on diet therapy alone, and the percentage of these patients who used insulin increased to about 30%. Among Mexican Americans who had T2DM that was diagnosed more than 14 years earlier, approximately 40% used insulin therapy.11

As suggested by the NHANES III11 results, diet therapy alone is often not effective for management of recently diagnosed T2DM. Many patients with T2DM would likely derive benefit from the initiation of combination drug therapy—along with lifestyle changes—during the 5-year postdiagnosis period. Moreover, several studies offer evidence of the benefits of certain medications for individuals in the prediabetes stage, including patients with metabolic syndrome.12

A Diabetes Outcome Progression Trial (ADOPT)13 examined how long each of three medications caused decreased HbA1c levels in patients who had recently diagnosed T2DM. More than 4000 patients (at trial outset) were treated with either metformin, glyburide, or rosiglitazone maleate (a TZD) for a median of 4 years. Patients using rosiglitazone maintained the lowest HbA1c levels during the study period. The results represented risk reductions for rosiglitazone of 32%, compared with metformin, and 63%, compared with glyburide (P < .001 for both comparisons).13 The ADOPT13 study suggests that patients using TZDs can achieve HbA1c reductions that have greater durability than those achieved with other medications.

Influencing the selection of initial medication for a patient with T2DM is the individual’s HbA1c level at presentation. For example, if the HbA1c start point is about 7.8% (as in the current case), a reduction of almost 2% in HbA1c is required to reach the ADA goal of as close to normal (<6%) as possible without causing hypoglycemia.9 Such a reduction implies a fairly robust modality of treatment.

The other treatment goals that need to be met for patients with T2DM are a preprandial plasma glucose level of 90 to 130 mg/dL, a peak postprandial plasma glucose level of less than 180 mg/dL, and a blood pressure reading of less than 130/80 mm Hg.9 Patients with nephropathy should have even lower blood pressure readings.

The initial therapy for Julio is detailed in Figure 2. He was placed on a low-protein diet and a walking program. The following medications were prescribed: pioglitazone hydrochloride (a TZD, 30 mg/d); irbesartan (an angiotensin receptor blocker [ARB], 150 mg/d titrated to 300 mg/d); hydrochlorothiazide (an antikaliuretic agent, 12.5 mg/d); and aspirin (325 mg/d).

The benefits of a walking program (or other frequent exercise) for patients with T2DM were clearly demonstrated by the Insulin Resistance Atherosclerosis Study (IRAS).14 That study evaluated the
effects of exercise frequency on insulin sensitivity and fasting insulin in more than 1400 adults with T2DM, including a substantial number of Mexican Americans. The results showed that as the number of exercise periods per week increased from zero to more than five, insulin sensitivity and fasting insulin levels increased in patients. Insulin sensitivity was greater by almost one third in patients who exercised at least 5 times per week than in patients who were sedentary. Thus, IRAS strongly suggests that adult patients with T2DM benefit from exercising more often—not necessarily more intensely or for longer durations.

Complication Considerations
Microvascular and Macrovascular Issues
As previously mentioned, Julio had diagnosed diabetic peripheral neuropathy, background retinopathy, and diabetic nephropathy with macroalbuminuria. Research to date has not uncovered a clear answer as to whether Hispanic individuals have a higher incidence of diabetic peripheral neuropathy than do individuals of other ethnicities.

Sands et al analyzed the number of cases of diabetic peripheral neuropathy per 100 person-years in 164 Hispanic subjects and in 67 non-Hispanic white people. These researchers concluded that the risk of neuropathy was essentially the same in each ethnic group—5.3 cases per 100 person-years in Hispanic people versus 5.0 cases per 100 person-years in non-Hispanic white people.

It is well known, through reports by the Joslin Clinic, that Hispanic people and African Americans have disproportionate risks of microvascular and macrovascular complications from T2DM. The prevalence of lower leg amputations, retinopathy and blindness, stroke, and end-stage renal disease is two to six times greater among individuals with T2DM in minority populations than in the white population. The reasons for these increased risks in minority groups are complex and not entirely known, though differing degrees of insulin resistance among different ethnicities undoubtedly plays a role.

Coronary Heart Disease—Hispanic people also have greater rates of cardiac-related mortality than do non-Hispanic white people in the United States. Pandey et al examined the mortality rates of coronary heart disease as recorded on death certificates in a small county in Texas. In comparing the recorded mortality rates for 785 Mexican Americans and 862 non-Hispanic white persons, the researchers determined that the number of deaths attributed to validated coronary heart disease was 36% greater among Mexican American women than among non-Hispanic white women. This association reached a level of statistical significance, with a rate ratio of 1.43 (95% confidence interval, 1.12-1.82).

Pandey et al also found that the number of deaths attributed to validated coronary heart disease was 12% greater among Mexican American men than among non-Hispanic white men. However, that association did not achieve a level of statistical significance. The greater risk of cardiac-related death among Mexican American women and men may be related to a number of factors, including multiple myocardial infarctions and complicated obesity.

Orlander et al analyzed the post-myocardial infarction survival rate among 610 Mexican Americans and 589 non-Hispanic white persons, including individuals with and without T2DM. The investigators found that—regardless of whether they did or did not have T2DM—Mexican Americans had greater mortality from myocardial infarction than did non-Hispanic white people. These results support the conclusion that the Hispanic population has multiple complicating risk factors for both T2DM and coronary heart disease.

The Troglitazone in Prevention of Diabetes (TRIPOD) study is one of the few cardiac/T2DM-related studies that consisted of exclusively Hispanic patients. This study analyzed the effects of the insulin-sensitizing agent troglitazone (400 mg/d) on several parameters in 93 Hispanic women with previous gestational T2DM, compared with 99 Hispanic women with previous gestational T2DM who were given placebo.

One of the parameters analyzed in the TRIPOD study was carotid intima media thickness (IMT), a surrogate marker for atherosclerosis. The researchers reported that the women using troglitazone had a significant reduction, or improvement, in their carotid IMT after 4 years, compared with placebo (P = .05). Thus, insulin sensitivity plays an important role in the Hispanic population in terms of macrovascular complications of T2DM, indicating that TZDs (ie, insulin sensitizers) would be effective in treatment.

Diabetic Nephropathy and Hypertension—It will be recalled that Julio had diagnosed diabetic nephropathy (with macroalbuminuria) and hypertension. Laboratory tests revealed a 24-hour urine creatinine clearance rate of 46 mL/min and an albumin shedding rate of 1.15 g/24 h, with a serum creatinine level of 1.7 mg/dL (Table). His blood pressure was 144/86 mm Hg. These conditions obviously developed in this patient over several years.

In consideration of Julio’s nephropathy, our goal was to safely reduce his blood pressure beyond the 130/80 mm Hg target of the ADA guidelines. To achieve such a goal with an individual who has a systolic blood pressure greater than 140 mm Hg or a diastolic blood pressure greater than 90 mm Hg, both behavioral and drug therapy—typically involving a combination of medications—are called for.

Investigators with the Heart Outcomes Prevention Evaluation (HOPE) study examined the effects of the angiotensin-converting enzyme (ACE) inhibitor ramipril (10 mg/d) versus placebo on more than 3000 patients who had T2DM, focusing on the following endpoints: myocardial infarction, stroke, cardiovascular death rate, overt nephropathy, and all these events combined.

The HOPE investigators concluded that the use of ramipril led to significant improvements in all the analyzed events, with P values ranging from less than .001 to .027. Thus, an ACE inhibitor might have proven effective for the current patient. However, we instead chose to
use irbesartan, based in part on the results of the Irbesartan Diabetic Nephropathy Trial (IDNT).22

The IDNT22 was one of the main trials that led to the approval of irbesartan, an ARB, by the US Food and Drug Administration. Investigators with IDNT randomly assigned 1715 hypertensive patients with T2DM-related nephropathy to receive irbesartan (300 mg/d), amlodipine besylate (10 mg/d), or placebo. These groups were compared for times to reach the following endpoints: doubling of baseline serum creatinine concentration, development of end-stage renal disease, or death from any cause.

The IDNT researchers found that the risk of doubling of serum creatinine concentration was 33% lower in the irbesartan group than in the placebo group (P=.003) and 37% lower in the irbesartan group than in the amlodipine group (P<.001).22 Irbesartan was also linked with a relative risk of end-stage renal disease that was 23% lower than in the other groups (P=.07).23 The IDNT strongly suggested that ARBs are appropriate for individuals who have macroalbuminuria and elevated creatinine levels, such as the patient in the current case.

The ADA treatment guidelines for patients who have hypertension and nephropathy include optimizing glucose and blood pressure control to slow the progression of the nephropathy.9 Excess glucose and high blood pressure are two of the most important contributors to advancing retinopathy and renal disease. Toward this end, a patient’s serum creatinine level needs to be measured at least annually.

The ADA also recommends that protein intake be limited to less than 0.8 g/kg in patients who have chronic kidney disease.9 For patients with albuminuria, treatment with an ACE inhibitor orARB is indicated; if a medication in one of these classes is not tolerated, then a drug from the other class should be used.9 In all patients receiving ACE inhibitors, ARBs, or diuretics, renal function and serum potassium levels need to be closely monitored.9 It is essential to guard against the potential development of hyperkalemia when using these medications.

Based on his creatinine clearance rate of 46 mL/min, Julio had stage 3 chronic kidney disease.23 The National Kidney Foundation defines stage 3 chronic kidney disease as a glomerular filtration rate between 30 and 59 mL/min/1.73 m2.23 Without receiving aggressive treatment, this patient would be at risk for the development of end-stage renal disease and the need for dialysis. Additional laboratory tests that might prove useful in this case include measurements of parathyroid hormone and 25-hydroxy (25-OH) vitamin D. Additional interventions might include paricalcitol (a vitamin D analog)—which can reduce parathyroid hormone and secondary hyperparathyroidism—and evaluation by a nephrologist.

To evaluate the severity of PVD in Julio, a treadmill test and ankle-brachial index (ABI) test were done. In an ABI test, blood pressure is measured at the ankle and arm while an individual is at rest, and then again after 5 minutes of walking on a treadmill. Hamdy et al24 reported that substantial improvements in PVD (ie, increased brachial artery diameter) can be obtained in patients with T2DM through 6 months of weight reduction and exercise, regardless of degree of glucose tolerance. It is also important to note that any correction in insulin resistance, glycemia, or related factors can lead to improvements in a patient’s peripheral vascular component.

In the current case, the treadmill test revealed no signs of angina, though the patient did report intermittent claudication (ie, pain in the calf, thigh, or buttock), and the ABI test suggested left-sided PVD. A stent was placed in Julio’s partially occluded femoral artery. In addition, his antiplatelet therapy was switched from aspirin to clopidogrel (75 mg/d), because the aspirin caused gastrointestinal intolerance. Elements of Julio’s revised treatment plan appear in Figure 2.

Hyperlipidemia

Additional pharmacologic intervention was required to address Julio’s severe hyperlipidemia—total cholesterol, 228 mg/dL; LDL-C, 146 mg/dL; HDL-C, 32 mg/dL; triglycerides, 250 mg/dL (Table). None of these lipid levels were even close to target. The ADA guidelines for individuals with T2DM call for an LDL-C level of less than 100 mg/dL, HDL-C levels of greater than 40 mg/dL in men and greater than 50 mg/dL in women, and a triglyceride concentration of less than 150 mg/dL.10 In very high-risk patients (eg, those with both T2DM and cardiovascular disease), an LDL-C goal of less than 70 mg/dL is preferred.25

As demonstrated by the Heart Protection Study,26 administering a hydroxymethylglutaryl-coenzyme A reductase

Figure 2

Hyperlipidemia

Additional pharmacologic intervention was required to address Julio’s severe hyperlipidemia—total cholesterol, 228 mg/dL; LDL-C, 146 mg/dL; HDL-C, 32 mg/dL; triglycerides, 250 mg/dL (Table). None of these lipid levels were even close to target. The ADA guidelines for individuals with T2DM call for an LDL-C level of less than 100 mg/dL, HDL-C levels of greater than 40 mg/dL in men and greater than 50 mg/dL in women, and a triglyceride concentration of less than 150 mg/dL.10 In very high-risk patients (eg, those with both T2DM and cardiovascular disease), an LDL-C goal of less than 70 mg/dL is preferred.25

As demonstrated by the Heart Protection Study,26 administering a hydroxymethylglutaryl-coenzyme A reductase
inhibitor (ie, statin) can result in substantial reductions in a patient’s LDL-C levels and cardiovascular risk. Other lipid-correcting pharmacologic options include niacin, fenofibrate, and fish oil (ie, omega-3 fatty acids).

According to NCEP guidelines, the first goal in lipid management is to lower LDL-C levels, to be followed by addressing HDL-C and triglyceride concentrations. The American Heart Association notes the value of consuming fish and omega-3 fatty acids for correcting triglycerides and, to a lesser extent, HDL-C.

In the current case, Julio was started on therapy with simvastatin (20 mg/d) at 3 months into treatment, with the expectation that it would result in approximately a 30% reduction in his LDL-C level. He was also given niacin (1 g/d) to help increase his HDL-C level (Figure 2).

Simvastatin (20 mg/d titrated to 40 mg/d) was shown to reduce both mortality and cardiovascular events, compared with placebo (P=.08 and P=.002 respectively), in a subgroup of 202 patients with T2DM in the Scandinavian Simvastatin Survival Study. Those results indicate that statins are useful not only in reducing LDL-C levels, but also in improving patients’ cardiovascular conditions and survival rates—the clinical endpoints that matter the most.

**Depression**

Another complication that often needs to be addressed in patients with T2DM is depression. Egede et al examined how the coexistence of T2DM and depression—compared with the lack of T2DM, depression, or both—affected the 8-year survival rates of 10,000 patients in the NHANES I Epidemiologic Follow-up Study. This analysis revealed that the mortality rate per 1000 person-years was highest in the patient group with both T2DM and depression. The patients in this group had a mortality rate after 8 years that was 30% to 40% greater than patients who had neither T2DM nor depression.

Many physicians do not consider evaluations of depression when developing treatment plans for patients with T2DM. However, as suggested by Egede et al, it may be extremely important for a patient’s long-term survival to identify and manage depression associated with T2DM.

**Case Follow-up and Related Issues**

The results of laboratory tests and other pertinent findings at 3-month, 6-month, and 9-month follow-ups in the current case are shown in the Table. By the 3-month follow-up, pioglitazone hydrochloride (30 mg/d), the glucose-lowering agent in Julio’s initial treatment plan, led to a reduction in his HbA1c level from 7.8% to 7.1% and in his fasting plasma glucose level from 169 mg/dL to 140 mg/dL. With the addition of sitagliptin phosphate (50 mg/d) to the treatment plan at the 3-month follow-up, Julio’s HbA1c level decreased to 6.4% by the 6-month follow-up. This 6-month HbA1c level was near our target value of 6%.

The use of simvastatin (20 mg/d) and niacin (1 g/d) led to substantial improvements in Julio’s lipid profile by the 6-month follow-up. The LDL-C level decreased from 146 mg/dL to 72 mg/dL, while the HDL-C increased from 32 mg/dL to 44 mg/dL (Table). Triglyceride concentrations (not shown) also improved substantially. Furthermore, it should be noted that the use of niacin did not result in a deterioration in the patient’s glycemic control—a possible complication that has sometimes been overstated in the literature.

These follow-up laboratory results make it clear that the use of an insulin-sensitizing agent (pioglitazone), a DPP-IV inhibitor (sitagliptin), and agents to manage lipid levels (simvastatin, niacin) successfully improved Julio’s glucose and lipid profiles.

Regulatory trials also support the effectiveness of using DPP-IV inhibitors with insulin-sensitizing agents. Rosenstock et al reported that the use of sitagliptin phosphate (100 mg/d) with pioglitazone hydrochloride (30 or 45 mg/d) caused HbA1c levels to remain close to target over 24 weeks for a group of 163 patients with T2DM, compared with the use of placebo and pioglitazone in a group of 174 patients with T2DM (P<.001). That study highlighted the augmented, or additive, effect that one medication can have on another in terms of glycemic control.

Most clinical trials of DPP-IV inhibitors do not include subgroup analyses on the safety and effectiveness of these medications in particular ethnic groups, such as the Hispanic or African American populations. This is an important factor to keep in mind because, for example, drug approval studies in Europe may not accurately reflect the ethnic diversity of the US population, leaving safety and efficacy questions regarding US minority groups unanswered. Yet, this missing information can be clinically relevant. More data are needed on the use of DPP-IV inhibitors for treating Hispanic, African American, and other US minority groups.

Two DPP-IV inhibitor studies that were fairly reflective of the US population in terms of the Hispanic population were Bosi et al and Hermansen et al.

Bosi et al analyzed the effects of the DPP-IV inhibitor vildagliptin on glucose control in patients with T2DM who were inadequately treated with metformin. The patient population in this study was 16% (67/416) Hispanic, which is close to the Hispanic makeup of the total US population (13%). The researchers found that vildagliptin was well tolerated and produced clinically meaningful decreases in HbA1c and FPG levels as add-on therapy.

Hermansen et al studied the use of sitagliptin as add-on therapy to glimepiride alone and to glimepiride with metformin. The patient population in that study was also 16% (71/441) Hispanic, closely reflecting the total US population. The investigators concluded that the addition of sitagliptin was generally well tolerated, with a modest increase in hypoglycemia and body weight.

Although neither Bosi et al nor Hermansen et al conducted a subgroup analysis, the fact that their patient samples accurately reflected the ethnic makeup of the US population made their results more meaningful for Hispanic patients. These are the types of studies that have the greatest clinical value when
prescribing medications for patients in the Hispanic and other minority populations.

There is another aspect of DPP-IV inhibitor use that may be clinically important for some patient populations: varying effectiveness depending on age. Some unpublished studies have indicated that the HbA\textsubscript{1c}-lowering effects of DPP-IV inhibitors may be more pronounced in patients who are older than 65 years than in younger patients. Such findings imply that decreasing insulin secretion is more clinically relevant in elderly patients than increasing insulin resistance.

Additional follow-up findings for Julio are presented in the Table. Irbesartan (150 mg/d titrated to 300 mg/d) and hydrochlorothiazide (12.5 mg/d) produced substantial improvements in the patient’s blood pressure, which showed a decrease from 144/86 mm Hg at his initial visit to 122/76 mm Hg at the 6-month follow-up. The 24-hour urine study repeated at his 6-month follow-up found a creatinine clearance rate of 50 mL/min (compared with 46 mL/min at the initial visit) and an albumin-shedding rate of 250 mg/24 h (compared with 1.15 g/24 h at presentation). These encouraging creatinine and albumin results were made possible by achieving improvements in Julio’s glycemic control and blood pressure control.

There were notable improvements in Julio’s PVD at his 9-month follow-up. He reported being able to walk 1 mile per day without having claudication. His hs-CRP level was reduced to 0.5 mg/L, compared with 3.2 mg/L at presentation—suggesting substantial improvements in his inflammatory background condition.

Also at the 9-month follow-up, Julio showed mild improvements in his diabetic peripheral neuropathy, with lack of pain and normal serum vitamin B\textsubscript{12} levels. An eye examination repeated at 9-month follow-up revealed that his background retinopathy remained stable. Julio reported important progress regarding his diet and weight at 9-month follow-up, including no longer snacking on peanuts, reducing his fruit intake, losing 12 lb in body weight, and being enthusiastic about his exercise regimen. Psychologically, this patient had transitioned from a person with a generally negative attitude about his health to an individual with a positive frame of mind regarding proper healthcare—the kind of clinical result that every physician hopes for.

Other Issues

Three issues that may require further exploration in regard to the Hispanic population with T2DM are obesity, non-alcoholic steatohepatitis (NASH), and sleep apnea. In the overall US adult population, the obesity rate is approximately 40%, and the overweight rate is about 65%. However, almost 80% of the Hispanic population in the United States is obese or overweight. Intriguing forms of therapy that this population may benefit from, in some cases, include gastric bypass, gastric stapling, and gastric balloon procedures.

As noted by Browning et al, NASH associated with obesity and T2DM is postulated to be the cause of most cases of cryptogenic cirrhosis. Browning et al reported that the prevalence of cryptogenic cirrhosis among Hispanic patients was three-fold higher than among European American patients. This finding indicates that many in the Hispanic population may have extensive intrahepatic fats and other liver abnormalities that could be associated with their insulin resistance and diabetic complications.

A number of recent studies have proposed an association between obstructive sleep apnea (OSA) and insulin resistance. For example, based on their review of the literature, Tasali et al noted that physicians need to address the risk of OSA in patients with T2DM and also evaluate the presence of T2DM in patients with OSA.

These are some of the important issues that physicians should keep in mind when examining Hispanic patients who have T2DM.

Comment

The patient in the current case—a Hispanic man 62 years of age—had newly diagnosed T2DM, obesity, diabetic peripheral neuropathy, background retinopathy, and diabetic nephropathy. He also had hypertension, peripheral vascular disease, and hyperlipidemia. A treatment plan including a low-protein diet, a walking program, pioglitazone, sitagliptin, irbesartan, hydrochlorothiazide, clopidogrel, simvastatin, and niacin proved successful in glycemic and lipid control, as well as in management of blood pressure, creatinine clearance rate, macroalbuminuria, peripheral vascular disease, diabetic peripheral neuropathy, and background retinopathy.

As the number of Hispanic Americans with diagnosed diabetes mellitus is projected to increase by 107% by 2020, improved diagnosis and management of T2DM and its complications in this population are vital to public healthcare.

References


