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Dyslipidemia Management in Diabetic Patients: A Case Report

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Abstract

A 60-year-old female patient was seen for follow-up of type II diabetes mellitus, hypertension, and dyslipidemia and was presently managing her dyslipidemia with 20 milligrams of atorvastatin. The U.S. Preventative Services Task Force (2016) recommends low to moderate-intensity statin therapy for this patient. However, the American Association of Clinical Endocrinologists and American College of Endocrinology (2017) guidelines, as well as the American College of Cardiology and American Heart Association's (2013) standards, recommend high-intensity statin therapy. Current research supports the use of high-intensity statin therapy for diabetic patients with other cardiovascular risk factors to obtain low-density lipoprotein (LDL) levels at or below 70 mg/dL. Research findings also support the use of ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors if high-intensity statin medications do not reduce LDL levels to goal. Fenofibrate therapy is an appropriate adjunct treatment for diabetic mellitus patients with dyslipidemia and triglyceride levels over 200 mg/dL and high-density lipoprotein (HDL) levels below 34 mg/dL. Niacin has not been proven to definitively improve cardiovascular outcomes in diabetic mellitus patients and in research trials it has been shown to increase diabetic complications, so this pharmacological treatment should not be routinely utilized among this patient population.

Keywords: diabetes, dyslipidemia, statin therapy

Dyslipidemia Management in Diabetic Patients: A Case Report

Atherosclerotic cardiovascular disease accounts for one-third of deaths in the United States and about 65% of diabetes-related deaths (Smith & Grundy, 2014; Chehade & Gladysz, 2013). Statin therapy has been the primary treatment method for individuals with dyslipidemia. However, differences exist in current practice guidelines regarding the intensity of statin treatment and whether statin dosing intensity should be based on cardiovascular risk factors, lipid panel results or a combination of these two variables. Current dyslipidemia guidelines also vary on their acceptance and recommendations for combination pharmacological treatment plans.

This case report will review the treatment of dyslipidemia in a 60-year-old female patient with type 2 diabetic mellitus who was presently taking 20 milligrams (mg) of atorvastatin but continued to have elevated levels of total cholesterol, triglycerides, and low-density lipoprotein (LDL) as well as decreased high-density lipoprotein (HDL). Current dyslipidemia guidelines are inconsistent, and treatment regimens vary between providers. New pharmacological treatment options are also being studied and may present excellent benefits for patients with diabetes mellitus. Therefore, current treatment approaches and guidelines for diabetic patients with dyslipidemia need to be examined.

Case Report

SJ is a 60-year-old Caucasian female with a history of dyslipidemia, hypertension and type II diabetes mellitus. For the last month, the patient had been experiencing numbness and tingling in her left great toe. Her blood pressure was elevated at 148/98, but the remainder of her vital signs were all within normal range. The patient verbalized a history of noncompliance with dietary and exercise recommendations, and she reported that she had difficulty with carbohydrate counting. She did not routinely monitor her blood pressure outside of the clinic, but she did

check her morning fasting blood glucose at home twice a week. The patient reported that her home blood glucose readings had been 150-200 mg/dL.

She denied any significant surgical history for herself. The patient's mother, father, and brother had a history of coronary artery bypass graft, but the patient did not have any personal history of cardiovascular complications. Her grandfather and her uncle had colon cancer, and she had a brother with type 2 diabetes mellitus.

SJ routinely attended dental and ophthalmology appointments. She was up-to-date on her Influenza vaccine and her mammogram. She was due for a colonoscopy and the pneumococcal 12 vaccine. It would also be recommended that this patient has a bone densitometry (DEXA) scan completed.

The patient was currently taking 500 mg of metformin, 81 mg of aspirin, 20 mg of lisinopril, 20 mg of atorvastatin and one tablet of a multivitamin daily. The patient did have an allergy to penicillin. She verbalized compliance with medications and denied any significant side effects including diarrhea, muscle pain, muscle discomfort, or gastric irritation. Currently, the patient denied any difficulty with affording medications.

The patient was alert, orientated and cooperative. On physical exam, the patient had a regular heart rate and rhythm without a murmur, click or rub. Chest expansion was symmetric, and her anterior and posterior lung fields were clear to auscultation bilaterally. No peripheral edema was noted, and peripheral pulses were 2+ bilaterally. Hair growth was visualized to bilateral halluxes, and her monofilament and vibration exams were within reasonable limits. Foot exam was positive for dry skin but absent of cracks and sores.

A comprehensive metabolic panel, a lipid panel, and a hemoglobin A1c (HgbA1c) were collected on this patient. Her HgbA1c was elevated at 7.8%, her fasting glucose was high at 138

mg/dL, and her glomerular filtration rate was decreased at 53 mL/min. Her total cholesterol was high at 220 mg/dL, triglycerides were also elevated at 186 mg/dL, her LDL was 110 mg/dL, and her HDL was low at 36 mg/dL. Her American College of Cardiology/American Heart Association's (ACC/AHA) 10-year primary atherosclerotic cardiovascular disease (ASCVD) risk score was 15.6%. All the remaining lab values were within normal limits.

The patient's medication was adjusted as follows, her atorvastatin was increased to 40 mg every evening, lisinopril was also increased to 40 mg daily, and her metformin will be slowly titrated to reach 1,000 mg twice daily. Detailed education on dietary and physical activity recommendations were reviewed with the patient, and a referral was made for a dietician appointment. The necessity for daily foot care was discussed with the patient, and a podiatry recommendation was made. The patient will follow-up in 3 months with a recheck of her HgbA1c and lipid panel at that time.

Literature Review

Dyslipidemia treatment guidelines vary among different healthcare organizations. Statin therapy has and continues to be the mainstay treatment for dyslipidemia; however, trials and research are being completed on numerous other pharmacological treatment options. SJ continues to have dyslipidemia despite moderate-intensity statin therapy. She did not complain of any side effects from her atorvastatin, so her atorvastatin was recently increased to high-intensity dosing. Research on the most appropriate treatment options and guideline recommendations will be discussed in detail to determine the most beneficial treatment approach for SJ and other diabetic patients with dyslipidemia.

Guideline Recommendations

Differences exist in current practice guidelines for the medication management of dyslipidemia in patients with diabetes mellitus. Presently the U.S. Preventive Services Task Force (2016) recommends treating diabetic patients with low to moderate-intensity statins when they are between the ages of 40 and 75 and have a calculated 10-year risk cardiovascular risk score of 10% or higher. The U.S. Preventive Services Task Force (2016) also stated that providers may consider utilizing a low to moderate-intensity statin for patients with a 10-year cardiovascular risk score of 7.5%-10%. Therefore, using the U.S. Preventive Services Task Forces' (2016) guidelines, no changes should have been made in the patient's atorvastatin dosing as she was previously on a moderate-intensity dosing regimen.

However, the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) classify diabetes mellitus as a significant atherosclerotic cardiovascular disease risk factor; therefore, diabetic patients with one additional risk factor are classified as very high-risk patients (Jellinger et al., 2017). This patient would be in the very high-risk category because she also has a diagnosis of hypertension. The AACE/ACE recommended treatment of dyslipidemia in very high-risk patients to goal levels of total cholesterol of less than 200 mg/dL, an LDL of less than 70 mg/dL and a triglyceride level of less than 150 mg/dL (Jellinger et al., 2017).

A high-dose statin is typically recommended to achieve these cholesterol levels, and a combination pharmacological treatment may be needed if the patient does not meet cholesterol treatment goals on a statin alone (Jellinger et al., 2017). Utilizing the AACE/ACE guidelines, this patient should be placed on a high-intensity statin, and her lipid levels need to be carefully monitored to evaluate whether she is meeting appropriate treatment cholesterol goals and to determine if additional pharmacological treatments are warranted.

The ACC/AHA's 2013 treatment of blood cholesterol recommendations advocates for moderate-intensity statin therapy in all patients between the ages of 40 and 75 with diabetes mellitus (Stone et al., 2013). They recommend increasing statin dosing to high-intensity for individuals with diabetes mellitus who have a 10-year ASCVD risk of greater than or equal to 7.5% (Stone et al., 2013). These guidelines do not recommend specific treatments to target goals for LDL management as the AACE/ACE guidelines do, and they also suggest against combination pharmacological therapy (Stone et al., 2013). The patient would be treated with the high-intensity statin when employing these guidelines due to her ASCVD risk level.

Cholesterol Goal Setting and Statin Intensity

The Cholesterol Treatment Trialists' Collaboration's (2010) meta-analysis examined 26 trials with a total of over 150,000 participants and found that the incidence of myocardial infarction and ischemic cerebrovascular accident could be reduced by 45-50% when LDL cholesterol was reduced by 2-3 mmol/L. The meta-analysis also found that high-intensity statin use reduced cardiovascular events by 15% and the frequency of major vascular events was directly proportionate to absolute LDL cholesterol reduction (Cholesterol Treatment Trialists' Collaboration, 2010). The researchers concluded that significant reductions in LDL were not associated with adverse events and suggested that it may be beneficial to utilize even lower LDL treatment goals for patients with elevated risk (Cholesterol Treatment Trialists' Collaboration, 2010).

Results of the Justification for the Use of Statin in Prevention: An Intervention Trial Evaluation Rosuvastatin (JUPITER) trial determined that when patients achieved LDL levels less than 70 mg/dL, a 44% reduction occurred in all vascular events, and a 20% decrease occurred in all-cause mortality (Ridker, 2009). Liu et al. (2016) found that high-intensity dosing

of atorvastatin improved diabetic patient outcomes when compared to moderate-intensity dosed atorvastatin. Boekholdt et al.'s (2014) meta-analysis analyzed eight high-quality dyslipidemia randomized control trials and found that LDL levels lower than 50 mg/dL were shown to significantly reduce cardiovascular risk when compared to patients with LDL levels between 75-100 mg/dL. These research findings all support the utilization of high-dose statin therapy instead of low or moderate-intensity statin therapy.

High-dose statin therapy has been shown to decrease LDL levels by 50% or higher; whereas, moderate-dose statin therapy reduces LDL levels by 30% to 50% (American Diabetes Association, 2017). SJ's LDL levels are currently 110 mg/dL and theoretically with high-dose statin use the patient's LDL levels should be reduced to around 55 mg/dL. This LDL level would be below the recommendation of 70 mg/dL, but would also be safe considering the findings of Boekholdt et al.'s (2014) and Cholesterol Treatment Trialists' Collaboration (2010).

Emerging Pharmacological Treatments

Statin use is associated with musculoskeletal pain in as many as 20% of outpatients taking this medication (Buettner, Davis, Leveille, Mittleman, & Mukamal, 2008). Due to muscle side effects, patients may be reluctant to take statins, or they may not adhere to statin dosing recommendations. Also, despite statin therapy, about 50% of United States diabetic patients fail to meet their LDL treatment goals (Sakamoto et al., 2015). Therefore, other pharmacological treatment options are available and should be considered for the treatment of dyslipidemia in patients with diabetes mellitus. Some of these pharmacological options include ezetimibe, fenofibrate, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and niacin.

Ezetimibe

Barkas et al. (2015) found that when utilizing high-intensity statins alone only 47% of patients achieved the ACC/AHA's treatment goal of a 50% reduction in LDL, but roughly 76% of patients met LDL goal recommendations when ezetimibe was added to statin treatment. Ezetimibe combined with atorvastatin 10 mg was shown to improve LDL goal achievement from 51% to 89.3% when compared to monotherapy with atorvastatin 20 mg for type 2 diabetic mellitus patients (Sakamoto et al., 2015).

The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) was a randomized, double-blind, placebo-controlled trial that enrolled 18,144 patients (Giugliano et al., 2017). The researchers found a 5% risk reduction in major cardiovascular events when adding ezetimibe to moderate-intensity simvastatin when compared to simvastatin alone for diabetic mellitus patients and found that the addition of ezetimibe reduced LDL cholesterol by roughly 24% (Cannon et al., 2015). Numerous studies have concluded that no meaningful changes in adverse events are seen when adding ezetimibe to a statin (Jellinger et al., 2017). Therefore, if after high-intensity statin use SJ's LDL remains above the goal of 70 mg/dL it would be appropriate to consider adding ezetimibe to her pharmacological treatment regimen.

Fenofibrate

Adding fenofibrate to statin therapy is another pharmacological treatment that has been utilized in the past. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial enrolled 10,251 patients between the ages of 40 and 79 who had a glycated hemoglobin level of 7.5% or higher and had cardiovascular disease or two cardiovascular risk factors (Action to Control Cardiovascular Risk in Diabetes Study Group, 2008). In the ACCORD study, 5,518 participants were randomly assigned to receive fenofibrate in addition to simvastatin (Action to Control Cardiovascular Risk in Diabetes Study Group, 2008). The study found that patients with

diabetic who were at elevated risk for cardiovascular events did not experience a reduction in cardiovascular events when fenofibrate was added to statin use (Action to Control Cardiovascular Risk in Diabetes Study Group, 2008). However, the follow-up study of the ACCORD trial found that fenofibrate may be beneficial in patients with type 2 diabetes mellitus who have triglyceride levels over 200 mg/dL and HDL levels less than 34 mg/dL (Elam et al., 2017).

Additionally, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial which enrolled 9,795 patients with type 2 diabetes mellitus between the ages of 50 and 75 with triglyceride levels over 200 mg/dL found an 11% reduction in secondary cardiovascular outcomes. (FIELD Study Investigators, 2005). Although SJ's current HDL level is low at 36 mg/dL and her triglycerides level is elevated at 186 mg/dL, the current research does not indicate that fenofibrate would be beneficial unless her triglycerides were over 200 mg/dL and her HDL was less than 34 mg/dL.

PCSK9 Inhibitors

PCSK9 inhibitor trials continue to be underway; however, available research findings indicate that diabetic patients who are at substantial risk for cardiovascular events can improve LDL reduction effects of statins from 36% to 59% when adding evolocumab or alirocumab to statin therapy (ADA, 2017). The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial was a randomized, double-blind, placebo-controlled clinical trial that enrolled 27,564 patients and examined the effects of adding evolocumab to statin therapy (Sabatine et al., 2017). The researchers found a 59% mean reduction in LDL when adding evolocumab to high-intensity statin use for high-risk patients (Sabatine et al., 2017).

The ODYSSEY COMBO II was a randomized, double-blind trial that enrolled 720 patients (Leiter et al., 2017). The purpose of the study was to compare the safety and effectiveness of alirocumab and ezetimibe (Leiter et al., 2017). The study found that after 12 weeks of alirocumab use 80% of patients with diabetes mellitus were at LDL goal levels of less than 70 mg/dL (Leiter et al., 2017). The study also examined diabetic complications from alirocumab and concluded that it did not affect fasting glucose levels or HgbA1c results (Leiter et al., 2017). Therefore, PCSK9 inhibitors may be an appropriate addition to this patient's treatment plan if she cannot reach LDL treatment goals despite high-intensity statin use or if she is unable to tolerate high-intensity statin dosing.

Niacin

HDL cholesterol is considered a protective factor against cardiovascular events independent of LDL levels (Brown et al., 2001). SJ's current HDL level is low at 36, so the provider may consider adding niacin to the patient's pharmacological regimen. The HDL-Atherosclerosis Treatment Study (HATS) enrolled 160 patients with decreased HDL but normal LDL levels and treated them with a combination of simvastatin and niacin (Brown et al., 2001). The study found that the rate of cardiovascular events was reduced by 90% when simvastatin and niacin were combined (Brown et al., 2001).

However, the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial enrolled 8,162 patients who were 45 years of age or older, had cardiovascular disease and low HDL and high triglyceride levels (AIM-HIGH Investigators, 2011). The participants were treated with simvastatin and niacin or simvastatin alone, and the study results found that although the

addition of niacin increased HDL levels and decreased triglyceride levels, no reduction in cardiovascular events occurred (AIM-HIGH Investigators, 2011).

The Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial found that among the 8,299 participants with diabetes mellitus, a 55% increase in severe disturbances in diabetes control occurred with patients who were treated with extended-release niacin (HPS2-THRIVE Collaborative Group, 2014). Due to the inconsistent research findings and the possibility of diabetic complications, niacin would not be an appropriate adjunct medication for this patient.

Learning Points

- High-intensity statin therapy should be utilized for patients with diabetes mellitus who also have other cardiovascular risk factors.
- LDL treatment goals of 70 mg/dL or less are appropriate for diabetic patients with additional known cardiovascular risk factors.
- Ezetimibe and PCSK9 inhibitors should be considered for patients on high-intensity statin therapy that continue to have LDL levels above treatment goal recommendations.
- Providers should consider initiating fenofibrate therapy for patients with diabetes mellitus and triglycerides levels above 200 mg/dL and HDL levels less than 34 mg/dL.
- Niacin therapy has not been shown to reduce cardiovascular events and may result in increased diabetic complications; therefore, it should not be utilized routinely in diabetic dyslipidemia management.

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