Pharmaceutical Treatment of Hypertension and Dyslipidemia in People With Diabetes: An Educator's Perspective Part 2: Dyslipidemia

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Case Presentation

T.S. is a 49-year-old, divorced, African-American man who was diagnosed with type 2 diabetes 4 years ago. He works as a court stenographer and is very active in community projects.

The patient is on oral medication for his diabetes. However, his blood glucose levels remain > 200 mg/dl. His hemoglobin A_{1c} (A1C) results have ranged between 8 and 9% over the past year. He denies symptoms of polyuria, polyphagia, polydipsia, or nocturia. He has no complaints of fatigue, blurred vision, chest pain, dyspnea on exertion, nausea, vomiting, diarrhea, constipation, early satiety, paraesthesias in his extremities, or burning pain in his feet.

There is no family history of diabetes. The patient's father died of myocardial infarction at age 55. His mother is alive and well.

Medications and supplements the patient uses include glyburide, 10 mg twice daily; zestril, 40 mg at bedtime; gingko; and a multivitamin.

T.S. has truncal obesity with a BMI of 39 kg/m^2. He lives alone, often skips breakfast, and eats most other meals out. He does not follow any kind of meal plan. Diet history reveals large portion sizes because of the frequent restaurant meals. His daily intake is 2,800 calories, of which 42% is fat, 15% is saturated fat, 15% is protein, and 43% is carbohydrate.

The patient says he is unable to do any exercise because his arthritic knees hurt him too much. He also states that he is too busy, and it is too dangerous to walk in his neighborhood because the dogs might attack him.

T.S. stopped smoking 15 years ago. Before that time, he smoked one pack of cigarettes per day for 10 years. He drinks one to two glasses of wine with dinner 5–7 days of the week.

Objective data and laboratory results:
Height: 5'8"
Weight: 258 lb
BMI: 39 kg/m^2
Blood pressure: 130/80 mmHg
Total cholesterol: 241 mg/dl
Triglycerides: 311 mg/dl
HDL cholesterol: 30 mg/dl
LDL cholesterol: 181 mg/dl
Fasting blood glucose: 198 mg/dl
A1C: 9%
Urine microalbumin: albumin/creatinine ratio: 48.7

Discussion

T.S. presented with hyperlipidemia, uncontrolled diabetes, microalbuminuria, poor nutrition, sedentary lifestyle, and truncal obesity. He has a family history of premature coronary artery disease and is at high risk for cardiac events.

This patient's lack of adequate diabetes control is evidenced by an A1C result of 9%, urine microalbumin: albumin/creatinine ratio of 48.7 mg/mg, and fasting blood glucose average of 198 mg/dl. After checking his liver and kidney function, the addition of metformin is indicated in order to lower his fasting blood glucose and to help decrease his overall A1C results. A follow-up A1C should be obtained in 3 months, at which time insulin may be considered if the result is not at the recommended goal of < 7%. T.S. should also be started on daily aspirin therapy immediately if there are no contraindications.

Because T.S. has multiple major risk factors for future cardiac events, his dyslipidemia should be treated aggressively. His total cholesterol, triglyceride, HDL cholesterol, and LDL cholesterol levels are all outside of the ideal goal range for patients with diabetes.

According to American Diabetes Association (ADA) guidelines, the first treatment intervention for dyslipidemia should be medical nutrition therapy (MNT) (Table 1) and physical activity.[1,2] The National Cholesterol Education Program Adult Treatment Panel III[3] emphasizes reduction in saturated fat, trans fats, and cholesterol and encourages moderate exercise. The panel also recommends that all individuals with dyslipidemia be referred to a dietitian.

If after 6 weeks the LDL goals are not met with dietary modification and physical activity, intensification of the therapeutic lifestyle changes should occur with reinforcement of saturated fat reduction, consideration of adding stanols/sterols, and increasing soluble fiber. Re-evaluation should occur in 6 weeks. Table 2 depicts the approximate and cumulative LDL cholesterol–lowering reduction achieved by dietary modification. In the presence of hypertriglyceridemia, alcohol consumption should also be evaluated.

Table 1. Highlights of ADA Guidelines for CVD Risk Reduction[1,2]

- Nutrient distribution: carbohydrate and monounsaturated fatty acids together should provide 60–70% of energy intake (E)*
- Saturated fat: < 10% total calories; < 7% for people with LDL cholesterol 100 mg/dl (A)*
- Cholesterol: < 300 mg/day; < 200 mg/day for people with LDL cholesterol 100 mg/dl (A)*
- Trans fats: minimize (B)*
- Total fat: Reduced-fat diets when maintained long term contribute to modest loss of weight and improvement in dyslipidemia (B)*
- Polyunsaturated fat: 10% of energy intake (C)*
- Fish meals: 2–3/week provide dietary omega-3 fats and can be recommended (B)*
- Energy balance: structured programs that emphasize lifestyle changes, including education, reduced fat (< 30% total kcal) and energy intake, regular physical activity, and regular participant contact can produce long-term weight loss of about 5–7% of starting weight (A)*

*ADA recommendations are evidence-based. A = clear evidence. B = supportive evidence from well controlled trials. C = supportive evidence from poorly controlled trials. E = expert consensus or clinical experience.

Physical activity opportunities should also be evaluated. Asking T.S. what options he sees for increased activity should be the introduction. Because safety has been identified as a concern, safe options should be discussed. These might include chair activities using exercise videos, use of a pedometer to increase the total number of steps taken each day, and potentially safe locations in which physical activity could take place.

If the initial LDL cholesterol level is > 130 mg/dl, or if the initial interventions are ineffective in improving lipid profiles, pharmacological therapy should be initiated.

Pharmacological Therapy of Dyslipidemia

Different available classes of lipid-lowering agents target various abnormalities. First-line agents for dyslipidemia include HMG CoA reductase inhibitors (statins), which target LDL cholesterol, and fibric acid derivatives (fibrates), which target triglycerides.

Second-line agents include bile acid sequestrants and nicotinic acid (niacin). Bile acid sequestrants have their greatest effect on lowering LDL and total cholesterol, and niacin is the only agent that targets all of the lipid disorders seen in diabetes. Although niacin has been traditionally contraindicated in individuals with diabetes because of its tendency to increase glucose levels, recent studies have demonstrated that it may be used with caution.

For patients with combined hyperlipidemia, the first choice in pharmacological treatment should be a high-dose statin. A fibrate in combination with a statin should be the second choice in therapy. It is important to be aware that any combination treatment involving statins puts patients at an increased risk for rhabdomyolysis and should be monitored accordingly.

Table 2. Approximate and Cumulative LDL Cholesterol Reduction Achievable by Dietary Modification[3]

Dietary Component	Dietary Change	Approximate LDL Reduction (%)
Major options		
• Saturated fat	< 7% of calories	8–10
• Dietary cholesterol	< 200 mg/day	3–5
• Weight reduction	Loss of 10 lb	5–8
Other LDL-lowering options		
• Soluble fiber	5–10 g/day	3–5
• Plant sterol/stanol esters	2 g/day	6–15
Cumulative estimate		20–30

The third choice in the treatment of hyperlipidemia should be a combination of a bile acid sequestrant and a fibrate. Bile acid sequestrants may bind and inhibit the absorption of fenofibrate. Therefore, fenofibrate should be taken 1 hour before or 4–6 hours after taking these agents.

The fourth choice in pharmacological therapy is the combination of a statin and niacin, with careful monitoring of glycemic control. Again, it is important to note the increased risk for rhabdomyolysis associated with statin combinations.

The individual drug classes are discussed in the remainder of this article. In addition, Table 3 provides a complete listing of medications by class, providing information about dosing recommendations, side effect profiles, and special considerations.

Statins

Statins are lipid-lowering agents that act primarily in the liver by inhibiting the enzyme HMG CoA reductase and by inhibiting cholesterol synthesis. This class of drugs also acts by increasing the number of hepatic LDL receptors on the cell surface in order to enhance the uptake and catabolism of LDL particles.

Statins should be used as adjunct therapy to diet in order to reduce total cholesterol, apolipoprotein B, LDL cholesterol, and triglycerides. Doses of statins should be chosen based on patients' level of hyperlipidemia, concomitant medications, and co-morbid illnesses.

Liver function should be assessed in all patients before initiating therapy and 12 weeks after the start of therapy. Lipid levels should be evaluated on a regular basis, and doses should be titrated in order to bring lipids into the desired target range.

Statin doses should be discontinued if serum transaminase (ALT) is more than three times the normal level, in the presence of elevated CPK levels, if myopathy occurs, or if there is a predisposition to renal failure.

All of the statin medications with the exception of pravastatin and fluvastatin are metabolized by the CYP3A4 enzyme system and put patients at increased risk for drug-drug interactions. Pravastatin is not metabolized by CYP450 isozymes,

Table 3. Quick Reference Guide to Lipid-Lowering Medications

Brand Name	Generic Name	Starting Daily Dose	Maximum Daily Dose	Pearls	
HMG-CoA REDUCTASE INHIBITORS (STATINS): Indicated for lowering LDL and raising HDL					
Class side effects: headache, gastrointestinal upset, myalgia, rash, dizziness, insomnia, elevated transaminase, myopathy, and rhabdomyolysis with renal dysfunction.					
Monitor liver function before therapy and 12 weeks after start of therapy. Decrease if serum transaminase > 3x normal level. Discontinue if myopathy or elevated CPK occurs or if there is a predisposition to renal failure. Avoid noncomitant gemfibrozil.					
Contraindications: Active or chronic liver disease					
Crestor	rosuvastatin	20 mg	40 mg	Daily	**For all statins:**
Lescol XL	fluvastatin	20 mg	80 mg	Give at bedtime	
Lipitor	atorvastatin	10 mg	80 mg	Daily	Avoid grapefruit or grapefruit juice while on this product.
Pravachol	pravastatin	10–20 mg	40 mg	Daily	
Mevachor	lovastatin	10–20 mg	80 mg	Give with evening meal	
Zocor	simvastatin	20–40 mg	80 mg	Give at bedtime	
NICOTINIC ACID DERIVATIVE (NIACIN) AND STATIN COMBINATION					
Class side effects: flushing, headache, pain, pruritus, dyspepsia, flu syndrome, rash, asthenia, hyperglycemia, and hypotension.					
Advicor	niacin/lovastatin	500 mg/20 mg	1,000 mg/20 mg		
FIBRIC ACID DERIVATIVES (FIBRATES): Indicated for hypertrigyceridemia, with additional LDL-lowering effect					
Class side effects: gastrointestinal upset, abdominal pain, dyspepsia, gallstones, myopathy, and increased risk of hepatoxicity					
Lopid	gemfibrozil	600 mg, twice daily	600 mg, twice daily	Take 30 minutes before eating. Drug interaction with warfarin. (Monitor PT.)	
Tricor, Lofibra	fenofibrate	67 mg, twice daily, unless switching from another agent. Then start 200 mg daily. Lofibra has a 134-mg dose	200 mg	Also has LDL-lowering effect. Drug interaction with warfarin. (Monitor PT.) If combined with bile acid sequestrants, give 1 hour before or 4–6 hours after the bile sequestrant	
NICOTINIC ACID (NIACIN): Indicated for combined dyslipidemia					
Class side effects: flushing (tolerance improves over time), nausea, vomiting, flatulence, pruritis, peptic ulcer, heptatoxicity, hyperuricemia, gout, and dose-related hyperglycemia.					
Obtain baseline uric acid, liver function tests (ALT, AST). Test again 6–8 weeks after reaching 1,500 mg, 6–8 weeks after maximum dose, and periodically thereafter.					
Contraindications: Liver disease, renal disease					
Niacin	crystalline nicotinic acid (immediate release)	250 mg (usual dose 11.5–3 g in divided doses 2–3 times per day)	4.5 g	Flushing and pruritus more common with immediate-release niacin but may abate with time. Administer with aspirin (325 mg) and food. Monitor glucose levels, uric acid levels in patients with gout. Increase dose slowly every 4–7 days until 2 g, then every 2–4 weeks until 3 g if lipid profile not improved. Available without prescription.	
Niacin Time Release	sustained-release nicotinic acid	500 mg (usual dose 1–2 g)	2 g in divided doses	Monitor blood glucose levels, uric acid levels in patients with gout. Increase dose slowly every 1–2 weeks. Available without prescription. Rare fulminant hepatitis reported in some SR formulations.	
Niaspan	extended-release nicotinic acid	500 mg (usual dose 1–2 g)	2 g in single dose	Increase dose slowly every 1–2 weeks.	
If switching from crystalline to a sustained-release niacin, use a smaller dose to reduce risk of hepatoxicity. Titrate up slowly.					
BILE ACID SEQUESTRANTS: Indicated for lowering LDL					
Class side effects: Constipation, fecal impaction, aggravation of hemorrhoids, gastrointestinal disturbance, osteoporosis, deficiency in vitamins A, D, K or folic acid, increased bleeding, hypochloremic acidosis, rash, and oral or anal irritation					
Contraindications: dysbetalipoproteinemia or TG > 400 mg/dl					
Colestid	colestipol	2 g once or twice daily	Tablets, 6 g, or packets, 30 g		
Questran Light	cholestyramine	1–2 scoops/packets daily	6 scoops or packets		
2-AXETIDIONONE: Indicated for lowering LDL					
Contraindications: liver disease, pregnancy					
Zetia	ezetimibe	10 mg		Use as monotherapy or as a complement to statin therapy.	

COMBINATIONS: There is an increased risk of myopathy and rhabdomylosis with all combination therapy. Use caution. Monitor LFT, CK.
Statin and fibrate combination: effective for combined dyslipidemia. Ensure renal function; limit dose of the statin when combining; check CK level at baseline and re-check if symptoms of muscles soreness.
Statin and niacin combination: effective atherogenic dyslipidemia, increases HDL. Use smaller dose of niacin.
Fibrate and niacin combination: not well studied
Fibrate and bile acid sequestrant: combination: administer fibrate 1 hour before or 4–6 hours after bile acid sequestrant.

Reasonable steps have been taken to ensure the accuracy of the information presented. However, the American Diabetes Association cannot ensure the safety or efficacy of any product described in this table.

and fluvastatin is metabolized by CYP2D6. Therefore, neither is affected by CYP3A4 inhibition. Concomitant use of medications that are potent CYP3A4 inhibitors (cyclosporine, fluvoxamine, indinavir, nefazodone, nelfinavir, and ritonavir) should be avoided in patients taking all other statins for dyslipidemia.

It is also important to note the well-documented drug-food interaction involving the combination of statins and grapefruit juice. Grapefruit juice is known to inhibit CYP3A4 resulting in an accumulation of abnormally high levels of statins in the system. Advise patients against drinking grapefruit juice or eating grapefruit while on these medications.

Fibrates

Fibrates are specifically indicated for use in patients with hypertriglyceridemia. These medications act by decreasing serum triglycerides and VLDL cholesterol. Fibrates are also effective at increasing HDL cholesterol levels. Studies have shown that fibrates also slow the progression of atherosclerosis and, as a result, reduce the risk for cardiac events in patients with type 2 diabetes.

Gemfibrozil and fenofibrate are the two fibrates currently on the market. Both have similar effects on triglycerides and HDL cholesterol, as well as similar side effects and precautions. Both are generally well tolerated, but either may cause symptoms of gastrointestinal upset including abdominal pain and dyspepsia. Fibrates have also been shown to cause gallstones and symptoms of myopathy in some patients. They may also cause hepatotoxicity. Therefore, liver enzymes should be monitored periodically. Neither medication should be used in patients with severe liver disease.

Caution should be used in patients who take warfarin with fibrates. Both gemfibrozil and fenofibrate may interact with warfarin, which may necessitate a dose change in the anticoagulant. Patients' prothombin time (PT) should also be monitored closely.

One of the benefits of using gemfibrozil is that it is available generically and may decrease costs for patients. Fenofibrate has an additional LDL-lowering effect that gemfibrozil does not, and therefore is a good medication choice in patients who have elevated LDL cholesterol along with high triglycerides and low HDL cholesterol.

Small studies have shown that the effect of repaglinide in combination with gemfibrozil may potentiate the effect of the repaglinide, which may increase the risk of hypoglycemia. The same effect has been noted with rosiglitazone and gemfibrozil. Caution should be used when using these medications in combination. Careful glucose monitoring should be encouraged. Fenofibrate may be considered as an alternative to gemfibrizil. One would suspect that the potentiated effect may also apply to pioglitizone as well.[4,5]

Bile Acid Sequestrants

During the normal digestion cycle, bile acids are excreted via the bile duct from the liver and gall bladder into the intestine. At the completion of the digestion cycle, most of the bile is reabsorbed from the intestines and returned via the portal circulation to the liver. Only a very small amount of bile is seen in the normal serum.

Bile acid sequestrants bind the bile acids in the intestine forming a complex that is excreted in the feces. This non-systemic action results in partial removal of the bile acids from circulation, preventing their re-absorption. LDLs are then broken down to form bile acids in order to replace the bile acids that have been lost.

The bile acid sequestrants have numerous gastrointestinal side effects, including nausea, vomiting, bloating, and constipation, that may make them difficult to tolerate. These medications can also bind with other medications. Therefore, it is necessary to take other medications either 1–2 hours before or 4–6 hours after taking the bile acid sequestrant.

Niacin

Niacin is an effective medication for lowering lipids. It is indicated for combined dyslipidemia because it decreases triglycerides, VLDL cholesterol, LDL cholesterol, and total cholesterol and increases HDL cholesterol. Niacin blocks the release of free fatty acids and suppresses the hepatic release of VLDL particles, which can lower triglycerides and decreases the number of small, dense, atherogenic LDL particles. Niacin is also the most potent drug available to raise HDL levels.

The biggest drawback in using niacin is its side effect profile. High doses of niacin are needed in order to treat dyslipidemia. These may cause numerous adverse effects, including flushing, itching, gastroinstestinal upset, and increased liver enzymes, which may lead to hepatotoxicity.

Niacin is available in either immediate-release, sustained-release, or extended-release formulations. Immediate- and sustained-release formulations are available over the counter. It is important to note that the sustained-release formulation may have a higher risk for hepatotoxicity.

Immediate-release or crystalline niacin seems to have the most problems with flushing. The flushing associated with these formulations may subside after continued use. Taking niacin with food and an aspirin tends to decrease the symptoms, as well. Niacin should be started at a low dose, and any increases in dosage should be made very slowly in order to minimize adverse effects.

Extended-release niacin is available with prescription. It is associated with less flushing, and fewer incidences of hepatotoxicity were reported by patients using the prescription product.

Niacin has previously been relatively contraindicated in individuals with diabetes because its use may result in increased insulin resistance and hyperglycemia. Recent studies have shown, however, that extended-release niacin improves lipid levels in patients with type 2 diabetes with a minimal increase in glucose levels. The increase in glucose levels in these patients were effectively alleviated with an increase in anti-diabetic medications.[6]

Niacin is sometimes used in combination with statins for improved lipid-lowering action. When combining niacin with a statin, a smaller dose of niacin should be used in order to lower patients' risk of developing hepatotoxicity, myopathy, and rhabdomyolysis.

Combining lipid-lowering agents requires very close monitoring of liver function tests and creatinine kinase (CK) levels. It is important to obtain

baseline laboratory tests of renal function and liver function before initiating lipid-lowering agents. If patients complain of muscle soreness, the drugs should be discontinued, and the patients' CK levels should be checked.

2-Azetidinone

2-azetidinone is the newest class of drugs for lowering cholesterol. The drug ezetimibe selectively inhibits the intestinal absorption of cholesterol. It decreases the delivery of cholesterol to the liver and increases the clearance of cholesterol from the blood. Ezetimibe can be used alone or in combination with MNT and physical activity in order to lower total and LDL cholesterol. Ezetimibe also seems to work very well in combination with statins, because it complements their actions and provides additional LDL lowering. Ezetimibe is reported to be well tolerated and is a good choice in patients who are already taking a statin but have not yet achieved target LDL levels.

Conclusion

Patients with profiles similar to that of T.S. in our case study must have their dyslipidemia treated aggressively. Starting T.S. on a statin is indicated in order to lower his high LDL cholesterol. The use of a statin along with better blood glucose control may also lower his triglycerides. In the event that these measures alone do not control his triglycerides, the addition of a fibrate may be considered.

In addition, although the treatment of dylipidemias in patients with diabetes is crucial, there are many other aspects that also need to be considered for optimal patient care. The combination of therapeutic lifestyle changes, blood glucose control, anti-hypertensive therapy, anti-hyperlipidemia therapy, and behavioral modifications are also important. All of these aspects work synergistically and are essential in order to reduce the risk of complications for individuals with diabetes.

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References

[1]American Diabetes Association: Nutrition principles and recommendations in diabetes. *Diabetes Care* 27 (Suppl. 1):S36–S46, 2004

[2]Franz MJ, Bantle JP, Beebe CA, Brunzell JD, Chiasson JL, Garg A, Holzmeister LA, Hoogwerf B, Mayer-Davis E, Mooradian AD, Purnell JS, Wheeler M: Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications (Technical Review). *Diabetes Care* 25:148–198, 2002

[3]Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). May 2001. (NIH publication no. 01-3670). Available online at www.nhlbi.nih.gov/guidelines/

[4]Niemi M, Backman JT, Neuvon M, Neuvonen PJ: Effects of gemfibrozil, itraconazole, and their combination on the pharmacodynamics of repaglinide: potentially harzardous interaction between gemfibrozil and repaglinide. *Diabetologia* 46:347–351, 2003

[5]Niemi M, Backman JT, Granfors M, Laitila J, Neuvonen M, Neuvonen PJ: Gemfibrozil considerably increases the plasma concentrations of rosiglitazone. *Diabetologia* 46:1319–1323, 2003

[6]American Diabetes Association: Dyslipidemia management in adults with diabetes (Position Statement). *Diabetes Care* 27 (Suppl. 1):S68–S71, 2004

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