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Vascular Risk Reduction in Type II Diabetes Mellitus: Addition of a Fibrate to a Statin

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Abstract

Diabetes mellitus is associated with a high risk of vascular complications and potential death related to these complications (Elam et al., 2017). Reducing the risk for vascular disease is a major focus in diabetes treatment. Strategies for reducing vascular risk in diabetes have included weight management, blood glucose control, blood pressure control, and total cholesterol and LDL-C normalization. A case presentation of a 65-year-old female with uncontrolled type II diabetes mellitus on a statin as a single lipid lowering agent is discussed below and is the basis for the literature review. A literature review was done to ascertain if the addition of a fibrate to a statin is helpful in lowering vascular risk in adults with type II diabetes mellitus, in comparison to the use of a statin medication alone. The literature concludes that vascular risk can be reduced in a subset of adult patients with type II diabetes using combination fibrate and statin therapy. This information is useful in treating diabetic patients with continued dyslipidemia despite the use of statin monotherapy and lifestyle modifications.

Vascular Risk Reduction in Type II Diabetes Mellitus: Addition of a Fibrate to a Statin

Diabetes mellitus type II is a major health concern. Individuals with type II diabetes are at an increased risk for vascular disease and mortality related to vascular events including heart attack and stroke (Klempfner et al., 2014). Some of the factors implicated in the increased vascular risk in diabetic patients include increased triglyceride levels, decreased high-density lipoprotein cholesterol (HDL-C), and increased low-density lipoprotein cholesterol (LDL-C) levels (Goff et al., 2010). Therefore, vascular risk reduction targeting dyslipidemia in diabetic patients is an important factor in caring for patients with this disease. Current vascular risk reduction recommendations for adult diabetic patients include normalization of lipid profiles and blood sugars, as well as smoking cessation and weight loss (American College of Cardiology, 2017).

Current guidelines recommend the use of statin therapy in patients with diabetes and dyslipidemia to target LDL-C levels and decrease the risk of atherosclerotic cardiovascular disease, but do not routinely recommend the use of fibrates (American College of Cardiology, 2017). Fibrates have not been recommended related to previous implications of safety using gemfibrozil in conjunction with a statin. Fibrates are a group of medications that can reduce triglyceride levels and increase HDL-C levels (Chen et al., 2013). This review will focus on lipid control, particularly the use of fibrates in combination with statins to reduce overall vascular risk in adult patients with diabetes mellitus type II.

Case Report

The case used as a basis for this literature review is that of a 65-year-old male who presented for a six month follow up for diabetes. He had no complaints at the time of follow-up. He was taking glipizide 10mg daily, lisinopril 10mg daily, Toprol XL 50mg daily, Janumet 50-

1000mg twice daily, aspirin 81mg daily and a multivitamin daily. Glipizide had been started six months ago to help with normalization of his blood sugars. He had gained weight with the addition of Glipizide over the past six months, and his blood sugars were ranging from 170-200mg/dl fasting and non-fasting.

He had a medical history of obesity, hyperlipidemia, hypertension, diabetes mellitus type II, and actinic keratosis. His past surgical history included cataract repair, colonoscopy with colon polyp removal, and carpal tunnel repair. He had a family history of heart disease. He denied tobacco use and drank alcohol socially. His last tetanus immunization was over ten years ago, and he had never received a pneumonia vaccination. His last colonoscopy was completed more than ten years prior to his appointment.

A CBC, CMP, urine, and cholesterol panel were collected while fasting. His urine creatinine and microalbumin, as well as microalbumin/creatinine ratio were within normal range. His glucose was 324mg/dL and total bilirubin was 1.1mg/dL, with the remainder of his CMP within normal limits. His hemoglobin A1C was 9.5mg/dL. His total cholesterol was 133mg/dL, triglycerides were 167mg/dL, HDL-C was 39mg/dL, and LDL-C was 61mg/dL. His blood pressure was 138/80, pulse of 72, respiratory rate of 18, weight was 122kg (269lb) and BMI was 36.5. His physical exam was unremarkable.

The patient was instructed to discontinue glyburide since it had not improved his blood sugars and had led to weight gain; and to start Lantus insulin 10 units every night. He was instructed to check his blood sugars three times per day and keep a log of his results.

Immunizations were updated at his appointment, and a colonoscopy was ordered. He was also instructed to increase physical activity and to follow up for his diabetes in two weeks. He was

referred to the diabetes resource center for further education on management of diabetes and lifestyle modification education.

This patient's triglycerides were elevated above the normal range, and his HDL-C was sub-optimal. High triglycerides and decreased HDL-C are both risk factors for vascular disease, and as such should be kept within a normal range if possible (Goff et al., 2010). The purpose of this literature review is to ascertain whether the addition of a fibrate medication to a statin would be beneficial in vascular risk reduction in adults with diabetes mellitus type II.

Literature Review

Fibrate medications have been shown to decrease triglyceride levels and increase HDL-C levels (Chen et al., 2013). The use of fibrate medications alone for lipid control has been used in those with hypertriglyceridemia. The use of statin medications in those with mixed dyslipidemia has been traditionally used alone for lipid control in conjunction with lifestyle modifications to decrease vascular risk and prevent potential vascular complications that can lead to increased mortality. This is the treatment currently recommended by the American Diabetes Association, with the goal of normalization of LDL-C levels less than 100mg/dL (American College of Cardiology, 2017). In patients with diabetes, increased triglycerides and decreased levels of HDL-C are prevalent and have been associated with an increased risk of coronary artery disease and vascular disease (Lella & Indira, 2013). The review of the literature will attempt to conclude if the addition of a fibrate medication to a statin will further decrease vascular risk in comparison to the use of a statin alone in adults with diabetes mellitus type II.

A thorough search of the recent literature regarding vascular risk reduction and the use of combination lipid therapy was completed using several databases. These databases included

CINAHL, PubMed, and Academic Search Premier. Research articles were also found in the references listed in articles. A total of 10 research articles were used in this literature synthesis.

In a landmark study published in 2010 (Goff et al., 2010), the addition of fenofibrate to a statin was originally studied in patients with diabetes mellitus type II to determine its effectiveness in decreasing cardiovascular risk further than with the use of a statin alone. This study found that there may be potential benefits for patients with both high triglycerides at baseline and decreased HDL-C at baseline. There was not a decrease in the rate of cardiovascular events or death from cardiovascular events in the overall study group (Goff et al., 2010). This study became the basis for further study regarding the possible benefits of adding a fibrate to a statin in adults with diabetes mellitus type II and dyslipidemia.

Triglyceride Reduction

Elevated triglycerides are found commonly in diabetes mellitus type II. This increase in triglycerides leads to an increased risk for vascular disease. In turn, the reduction in triglyceride levels may lead to decreased risk of vascular disease in these patients (Chen et al., 2013). This may be most beneficial in adult patients with baseline fasting triglyceride levels greater than 170 mg/dl (Davidson et al., 2014).

Research supports the addition of fenofibrate to a statin in adults with diabetes mellitus type II, with a greater reduction in fasting triglyceride levels compared with the use of a statin alone (Davidson et al., 2014; Elam et al., 2017; Foucher et al., 2015; Goff et al., 2010; Lella & Indira, 2013; Reyes-Soffer et al., 2013). Post prandial reduction in triglyceride levels were also found with the addition of fenofibrate to a statin (Reyes-Soffer, 2013).

In contrast to the studies finding decreased triglyceride levels with the addition of a fibrate, one study did not find any added benefit in controlling triglyceride levels with the

addition of fenofibrate to rosuvastatin in comparison to an increase in rosuvastatin dosage from 5mg to 10mg per day (Chen et al., 2013). Although this was the finding, the study used a lower dose of fenofibrate at 80mg per day than is recommended for those with mixed dyslipidemia, which may have limited the outcomes of the study (Epocrates, 2019). The increased dose of rosuvastatin was also more expensive than continuing at the lower dose of rosuvastatin and adding fenofibrate (Chen et al., 2013).

The use of a fibrate in addition to a statin to reduce vascular risk requires further research to confirm adequate dosing. Further study of the choice of statin and dosage of statin would also be beneficial for guidance in applying the findings to practice.

Increase in HDL-C

Increased levels of HDL-C are considered cardioprotective (Epocrates, 2019). The addition of a fibrate to a statin in adults with diabetes mellitus type II has been found to increase HDL-C levels in recent studies (Elam et al., 2017; Foucher et al., 2015; Papademetriou et al., 2016). In one study, this was found to be particularly beneficial in decreasing vascular risk in those without chronic kidney disease at baseline (Papademetriou et al., 2016). This is important for adults at high risk for vascular complications, including adults with type II diabetes.

In contrast, other literature studies have not found any significant difference with the addition of fenofibrate to a statin, in comparison to increased statin dosage in achieving an increase in HDL-C (Chen et al., 2013; Lella & Indira, 2013). This highlights the importance of consistent dosing of a fibrate and appropriate study sample size in comparing the results of studies, as Chen et al. (2013) used a decreased dose of fenofibrate when compared to other studies, and Lella & Indira (2013) had a very small sample size. This may have contributed to the mixed results of these studies in comparison to the other literature reviewed.

HDL-C reduction in patients using combination fibrate and statin in comparison to statin alone may also vary according to the patients baseline HDL-C (Davidson et al., 2014). This is an important piece of information to further study in order to maximize the benefits of combination fibrate and statin use in practice situations.

Inflammation and Vascular Disease Outcomes

Progression of vascular disease can be stabilized, and inflammatory markers implicated in vascular disease can be decreased with the addition of a fibrate to a statin in adults with diabetes mellitus type II (Davidson et al., 2014; Klempfner et al., 2014; Krysiak, Gdula-Dymek, & Okopien, 2013). This stabilization can be found from the increase in HDL-C concentrations and decrease in triglycerides with the addition of a fibrate to a statin (Davidson et al., 2014; Klempfner et al., 2014; Krysiak et al., 2013). Lymphocyte release of interleukin 2, interferon 4, and tumor necrosis factor alpha were decreased in patients on simvastatin with the addition of fenofibrate for three months (Krysiak et al., 2013). The decreased release of the inflammatory mediators that are linked to vascular disease can lead to a decreased vascular risk in adult patients with a subsequent decrease in vascular events (Krysiak et al., 2013).

The addition of fenofibrate to atorvastatin was found to decrease carotid intima-media thickness (cIMT) in those over the age of sixty with a history of coronary artery disease and triglyceride levels greater than 170 mg/dl (Davidson et al., 2013). The study participants that were found to benefit most from this were adults with diabetes mellitus type II. (Davidson et al., 2013). This benefit was found with use of combination fenofibrate and atorvastatin after approximately three and a half months (Davidson et al., 2013).

Major cardiovascular events and mortality were found to decrease in patients with diabetes mellitus type II and acute coronary syndrome with the addition of bezafibrate to a statin

compared to statin use alone (Klempfner et al., 2014). Major cardiovascular events over thirty days were decreased, with a subsequent decrease in mortality and rehospitalization in these patients (Klempfner et al., 2014). In the ACCORD trial (Goff et al., 2010) as well as in an extended study of the patients in the ACCORD trial (Elam et al., 2017), there was a decreased rate of cardiovascular events in those with baseline hypertriglyceridemia and low HDL-C levels using fenofibrate in addition to a statin, compared to the use of a statin alone. This combination of baseline dyslipidemia is a prevalent finding in adults with diabetes mellitus type II. The findings from the literature reviewed conclude that there is a benefit to adding a fibrate to a statin in this population. Therefore, baseline triglyceride and HDL-C levels, as well as vascular disease at baseline are important factors to consider in determining the potential benefit of fibrate use in addition to a statin in adults with diabetes mellitus type II.

Safety

Safety has continued to be a concern in relation to the use of fibrates in combination with a statin (Papademetriou et al., 2017). Adverse events were found to be more prevalent in patients using gemfibrozil in combination with a statin (Tarantino et al., 2017). This is related to gemfibrozil's ability to increase the half-life of statin medications (Tarantino et al., 2017). The concern with this effect has been the adverse reaction of fibrates in causing rhabdomyolysis, liver toxicity, and increases in creatinine and renal injury (Papademetriou et al., 2017).

The studies reviewed in this literature review did not use gemfibrozil, but instead used fenofibrate or bezafibrate in combination with a statin. The addition of either fenofibrate or bezafibrate with a statin was not found to have significant adverse effects on creatinine level, liver toxicity, or increased rhabdomyolysis in the majority of the recent literature (Chen et al., 2013; Davidson et al., 2014; Elam et al., 2017; Foucher et al., 2015; Goff et al., 2010;

Klempfner et al., 2014; Krysiak et al., 2013; Lella & Indira, 2013; Papademetriou et al., 2017; Reyes-Soffer et al., 2013). Baseline levels of creatinine, liver function tests, and myopathy symptoms are important to gather prior to initiation of a statin alone or in combination with a fibrate, and were consistently gathered in the studies prior to study initiation (Chen et al., 2013; Davidson et al., 2014; Elam et al., 2017; Foucher et al., 2015; Goff et al., 2010; Klempfner et al., 2014; Krysiak et al., 2013; Lella & Indira, 2013; Papademetriou et al., 2017; Reyes-Soffer et al., 2013). One study did find an increase in incidence of adverse renal events with the addition of a fibrate to a statin in comparison to statin monotherapy, measured by an increase in creatinine levels (Davidson et al., 2013). The patients in this group did not require dialysis or kidney transplantation but were discontinued from the study following the adverse effect (Davidson et al., 2013). The addition of a fibrate medication to a statin, therefore, has been deemed safe in patients whose baseline labs did not indicate renal disease or liver function abnormalities.

Key Points

- Fenofibrate or bezafibrate can be used safely in combination with a statin for lipid control in adult patients with diabetes mellitus type II with no renal or liver impairment at baseline
- Fenofibrate in combination with a statin is beneficial in normalizing HDL-C and triglyceride levels in adult patients with diabetes mellitus type II.
- Fenofibrate in combination with a statin can reduce vascular risk in patients with diabetes mellitus type II with baseline hypertriglyceridemia and sub-optimal HDL-C levels.
- Fenofibrate use in combination with a statin should be used more frequently in adult patients with continued dyslipidemia despite statin use and lifestyle modifications.
- Additional long-term randomized controlled trials on the use of a fibrate in combination with a statin in adult patients with type II diabetes mellitus and baseline dyslipidemia would be beneficial to ascertain the most beneficial dosage and type of fibrate and statin combination to be used to provide the most benefit in reducing vascular risk.

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