2018

Comparing the Effectiveness of a Low Carbohydrate Diet and Metformin on Glycosylated Hemoglobin Reduction in Type Two Diabetes Mellitus

Ashley Schultz
University of North Dakota

COMPARING THE EFFECTIVENESS OF A LOW CARBOHYDRATE DIET AND METFORMIN ON GLYCOSYLATED HEMOGLOBIN REDUCTION IN TYPE TWO DIABETES MELLITUS

Ashley Schultz, B.S., PA-S

University of Minnesota Twin Cities

A Scholarly Project

Submitted to the Graduate Faculty of the

University of North Dakota

In Partial Fulfillment of the Requirements for the Degree of

MASTER OF PHYSICIAN ASSISTANT STUDIES

Grand Forks, North Dakota

Professor Daryl Sieg, PA-C

Scholarly Project Development – PA525

May 2018

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Acknowledgments

I would like to first and foremost thank God for guiding me through this challenging journey. Without Him, none of this would be possible. I would especially like to thank my family: Jake, Bella, Emerson, Mom, Dad, Tammy, and John for helping me coordinate my time to complete this project along with maintaining my sanity. All your love, patience, and support allowed me to accomplish this scholarly project. Thank you!

Abstract

In this study, a low carbohydrate diet and metformin pharmacotherapy were compared to determine their effect on HbA1c in the type two diabetic patient. Several high quality studies were examined along with each treatments effect on mainly HbA1c, but also other parameters such as body weight, cholesterol, and fasting and post prandial blood glucose levels. The study showed that both the low carbohydrate diet and metformin pharmacotherapy were effective at lowering HbA1c in the type two diabetic patient. The low carbohydrate diet showed a 0.2% increase in HbA1c all the way to a 2.2% decrease in baseline HbA1c in the studies that were examined. The metformin pharmacotherapy showed between a 0.45% decrease up to a greater than 1% decrease from baseline HbA1c in the studies examined within this project. After looking at the other parameters that were affected by each treatment, it was concluded that choosing treatment between the two options studied will be highly dependent on each individual patient and their readiness and willingness to implement lifestyle changes. Both methods of treatment are equally as effective and can be beneficial to different patients.

Keywords: type two diabetes mellitus, T2DM, glycosylated hemoglobin, HbA1c metformin, low carbohydrate diet

Introduction

In a country where obesity is on the rise and the number of newly diagnosed type two diabetics is exceeding 1.5 million patients each year, it is time to explore the most efficacious, lasting, and cost effective first line treatments (American Diabetes Association [ADA], 2017). According to the ADA (2017), type two diabetes mellitus (T2DM) is the seventh leading cause of death in the United States and approximately 9.4% of the American population are diagnosed with T2DM. There are several different medications available to treat diabetes, but what is often overlooked is the possibility of treating diabetes with diet and exercise. The American Diabetes Association (2017) also found that in 2012, approximately $245 billion was spent on direct medical costs and reduced productivity directly linked to T2DM. This is not only a serious health problem, but it is an economic problem as well.

The following research is comparing the effectiveness of a low carbohydrate diet and metformin on reducing a type two diabetic's HbA1c (HbA1c). According to DynaMed Plus (2017c), the HbA1c is a measure of the average amount of glucose in the past 120 days. The article describes that this can be measured because bonds are formed between glucose and hemoglobin (the portion of erythrocytes that contains iron and transports oxygen) and since the average lifespan of an erythrocyte is about 120 days, the glucose attached to the hemoglobin (HbA1c) can be measured for that time span. A diagnosis of T2DM requires a HbA1c reading of greater than 6.5% (DynaMed Plus, 2017a). The HbA1c contrasts with the blood glucose level that can be measured at any time and changes nearly instantaneously in relation to dietary intake.

Initial treatments for T2DM can include, but are not limited to, lifestyle changes and/or metformin. A patient that wishes to use lifestyle interventions will likely use a mix of dietary changes facilitated by a registered dietitian (Grade A recommendation), increased physical

activity to improve high density lipoprotein cholesterol levels (Grade B recommendation), and education from a diabetic educator (Grade B recommendation) (DynaMed Plus, 2017a). Metformin is a drug that is often used as initial pharmacologic therapy (Grade A recommendation) for T2DM (DynaMed Plus, 2017e). Metformin is an antihyperglycemic drug that lowers basal and postprandial blood glucose levels and does this by decreasing the production of glucose in the liver and decreasing intestinal absorption of glucose in the distal small intestine as described by DynaMed Plus (2017e).

As a medical provider seeing diabetics in the clinic setting daily, it is important to be able to present the patient with their options and the effectiveness of these options for decreasing their HbA1c. A patient should be well informed before he/she embarks upon this patient-provider joint decision making process.

Statement of the Problem

The number of T2DM patients continues to rise each year. Medical providers face the challenge of treating type two diabetes on a daily basis and there are numerous possibilities available as treatment options. Medical providers and patients need to be able to choose their first line treatment based on scientific evidence, effectiveness, and how that treatment will fit in with the patient's personal lifestyle. The low carbohydrate diet and metformin need to be compared in terms of effectiveness on HbA1c as the solo first line treatment of diabetes mellitus. This research will be able to guide medical providers and patients in selecting a treatment plan for T2DM.

Research Questions

In newly diagnosed type two diabetics presenting for initial treatment, does a low carbohydrate diet or metformin have a greater effect on lowering glycosylated hemoglobin?

What are the advantages of a low carbohydrate diet on lowering glycosylated hemoglobin?

What are the disadvantages of a low carbohydrate diet on lowering glycosylated hemoglobin?

What are the advantages of metformin pharmacotherapy on lowering glycosylated hemoglobin?

What are the disadvantages of metformin pharmacotherapy on lowering glycosylated hemoglobin?

There are several different pharmacotherapy and diet treatments that may benefit type two diabetics, but the two therapies that are going to be focused on in this project will be a low carbohydrate diet and metformin pharmacotherapy. The main parameter that will be studied is the effect on HbA1c, but there will also be some information regarding the treatment's effect on body weight, cholesterol, and fasting and post prandial blood glucose levels. The two treatments will be compared and both advantages and disadvantages will be explored to determine what recommendations and education can be given to patients diagnosed with T2DM.

Literature Review

Methodology

In researching the above mentioned topic, PubMed, CINAHL, and EBSCO were all utilized. In PubMed, MeSH terms were used in the following groupings: “Diabetes Mellitus, Type 2 AND Diabetes Mellitus, Type 2/diet therapy”, “Diabetes Mellitus, Type 2/diet therapy AND Diet, Carbohydrate-Restricted”, “Diabetes Mellitus, Type 2 AND metformin”, and “Diabetes Mellitus, Type 2 AND hemoglobin A1c protein, human AND metformin”. In CINAHL and EBSCO, the following search terms were used as groups: “Type 2 Diabetes Mellitus AND Low Carbohydrate Diet”, “Type 2 Diabetes Mellitus AND Glucophage AND A1c”, and “Type 2 Diabetes Mellitus AND metformin AND HbA1c”. When choosing publications to use for the research, peer reviewed articles within the past 10 years comprised the majority of the research used.

The literature review generated many high-quality research studies that explored the efficacy of the treatments for T2DM. The studies were focused around the low carbohydrate diet and metformin and their effectiveness of lowering HbA1c. Within these studies, other types of diets were also studied along with other pharmacologic treatments including dual therapy treatments for T2DM. Large studies organized around a low carbohydrate diet as solo treatment for type two diabetes are not widespread at this time. This is likely because of the known effectiveness of metformin. Although there isn’t an overabundance of studies on diet alone, this area of research will possibly increase with the increasing cost of healthcare, including pharmaceuticals.

Low Carbohydrate Diet Management of Type Two Diabetes Mellitus

Understanding the underlying pathophysiology of T2DM helps us to understand the theory behind treating type two diabetics with a low carbohydrate diet. Diabetes mellitus patients have an underlying disruption in the metabolism of carbohydrates according to Feinman et al. (2015). With this, there ends up being an increase of carbohydrates that are not metabolized which leads to hyperglycemia (Feinman et al., 2015). So knowing this, logically, if a person takes in less carbohydrates, there will be less carbohydrates left unmetabolized and therefore glycemic levels will be decreased.

Both Feinman et al. (2015) and Huntriss, Campbell, and Bedwell (2017) agree that the definition of low carbohydrate is not well defined in the research world. Feinman et al. (2015) goes on to define a very low carbohydrate ketogenic diet (VLCKD) as 20-50 g/d which is less than 10% of a 2000 kcal/d diet, a low carbohydrate diet is then defined as less than 130 g/d which is less than 26% of a 2000 kcal/d diet, a moderate carbohydrate diet is 26-45% of a 2000 kcal/d diet, and a high carbohydrate diet is defined as greater than 45% of a 2000 kcal/d diet coming from carbohydrates and Huntriss et al. (2017) set forth the same guidelines for categorizing carbohydrate diets.

Advantages of using diet management as first line treatment of type two diabetes mellitus. Of the several research studies available on the effects of a low carbohydrate diet on type two diabetics, the common parameters that seem to be studied and emphasized are the effects on HbA1c, plasma glucose, weight loss, and lipids. Although these will all briefly be touched on, the focus will remain on the effect of the low carbohydrate diet on lowering HbA1c.

The group of people that is most affected by T2DM is the obese group according to DynaMed Plus (2017a). Obesity is defined as having a body mass index (BMI) greater than 30 kg/m^2. (DynaMed Plus, 2017f) Because of the previous stated facts, a decrease in weight would

be a logical treatment for T2DM and this would be an additional benefit of using a low carbohydrate diet to treat diabetes. A few of the studies that were examined during this literature review looked at the effects of the low carbohydrate diet on weight loss as well as the HbA1c. Tay et al. (2015) looked at both high and low carbohydrate groups and found that the high carbohydrate diet group had a drop of 3.2 kg/m^2 ($P = 0.31$) in their BMI and the low carbohydrate group had a decrease of 3.5 kg/m^2 ($P = 0.31$) in their BMI. Tay et al. (2015) concluded both the high and low carbohydrate diet groups showed a substantial weight loss over the 52-week research study that was conducted. In the study done by Feinman et al. (2015), two diets were compared, a low carbohydrate diet and a generalized healthy eating diet. Between these two diets, there was an average of 6.9 kg ($P \geq 0.09$) of weight loss in the low carbohydrate group and a 2.1 kg ($P \geq 0.09$) weight loss in the healthy eating diet over a period of three months. This showed that the more structured and specific low carbohydrate diet had a greater influence on weight loss within this specific study. Kirk et al. (2008) concluded that there was no statistical difference in weight loss between the low carbohydrate diets and the control groups and they determined that this was due to the inconsistency of the goals of the studies that were being evaluated. Some of the studies being evaluated had a goal of weight stability throughout the trial while other studies were both low carbohydrate and hypocaloric which would result in weight loss. Finally, Huntriss et al. (2017) determined that at the end of the trial periods, five out of the 15 total studies included in their systemic review had a statistically significant increase in weight loss compared to the control group and none of the studies showed that the control group had a higher weight loss. It is important to note that Huntriss et al. (2017) excluded several studies due to them not providing sufficient information pertaining to the meta-analysis being conducted.

Another parameter that was studied in several of the studies was the effect of a low carbohydrate diet on the patient's cholesterol. Ajala, English, and Pinkney (2013) found that the low carbohydrate diet effectively raised the patient's high density lipoprotein cholesterol an average of 10% ($P < 0.00001$) over the studies included in their meta-analysis. In the same study, they found that the low density lipoprotein cholesterol was not lowered by the low carbohydrate diet. This study done by Ajala et al. (2013) excluded six studies from their meta-analysis because of two reasons. Four of the studies had insufficient evidence to compare to other studies within the subgroup and two of the studies included participants both with and without T2DM. Another study done by Kirk et al. (2008) did not see a big difference in high density lipoprotein cholesterol, low density lipoprotein cholesterol, or total cholesterol, but they did find a significant decrease in triglycerides. The study showed that decreasing carbohydrate intake from 65% to 35% resulted in an average of 23% decrease in the patient's triglyceride level. Feinman et al. (2015) had similar findings to Kirk et al. (2008) with no significant difference in low density lipoprotein cholesterol, high density lipoprotein cholesterol, or total cholesterol, but a decrease in triglycerides. Feinman et al. (2015) found that the low carbohydrate diet groups had an average decrease in triglycerides of approximately 22%. In a similar analysis done by Kodama et al. (2009) for the American Diabetes Association, they found that the high fat low carbohydrate diet had a decrease in triglycerides of 13.4% ($P < 0.001$, CI = 95%) compared to the low fat high carbohydrate group. A literature review conducted by Jung and Choi (2017) examined the differences of a high carbohydrate diet versus a low carbohydrate diet on many parameters including high density lipoprotein cholesterol, low density lipoprotein cholesterol, total cholesterol, and triglycerides. Within these metabolic parameters, the authors found no significant difference between the two diets in their ability to decrease low density lipoprotein

cholesterol and total cholesterol, but the low carbohydrate diet was more effective at lowering triglycerides and raising high density lipoprotein cholesterol. This added benefit of decreased triglycerides and possibly increased high density lipoprotein cholesterol contribute to the argument that a low carbohydrate diet would be beneficial for patients with T2DM.

Now moving closer to the problems specific to patients with T2DM, it is time to examine the research done on glycemic control (excluding HbA1c) and the effects that a low carbohydrate diet has on these measures. The study that was done for the American Diabetes Association by Kodama et al. (2009) again compared the low fat high carbohydrate diet to the high fat low carbohydrate diet and within this analysis, they found that the low fat high carbohydrate diet resulted in an increase of fasting glucose by 8.4% ($P = 0.02$, 95% CI = 7.2% to 9.6%). The study also found that the two-hour glucose and insulin values were higher in the low fat high carbohydrate group compared to the high fat low carbohydrate group by 10.3% ($P < 0.001$) and 12.8% ($P < 0.001$) respectively. Tay et al. (2015) found that patients who adhered to a low carbohydrate diet spent a lower amount of time in a hyperglycemic range and a greater amount of time in the euglycemic range. The study also showed that the amount of time spent in a hypoglycemic range did not differ from the low carbohydrate group and the control group.

After examining the other various advantages of having a patient with T2DM use a low carbohydrate diet, the effects of this diet on a patient's HbA1c can be examined.. The study done by Kirk et al. (2008) showed that the low carbohydrate diet groups decreased their HbA1c significantly with an average of 0.79%. The rates of decrease in the different studies included in their meta-analysis ranged from a 0.3% increase to a 2.2% decrease with only one study out of the eleven completed studies showing an increase of HbA1c. The original research study done by Yamada et al. (2014) also showed a significant decrease in HbA1c after a six-month trial period.

This study showed a decrease in HbA1c of 0.6% (P = 0.03) in the patients that were studied. Within this same study, the calorie restricted group showed no change in the HbA1c after the six-month study. A unique study was done not on a generalized low carbohydrate diet, but instead on substituting a multifunctional bread rich in beta glucans and also low in starch by Tessari and Lante (2016). This study showed that after six months of substituting the unique bread into the diets of the subjects, the functional bread group had a decrease of 0.52% (P = 0.028)in their HbA1c levels. A meta-analysis done by Huntriss et al. (2017) examined eighteen studies and at the end of the trials (which varied from three months to one year) twelve of the seventeen studies that were completed showed a decrease in HbA1c of more than 0.2% and of these studies, four of them had a decrease of more than 0.5%. Not all the studies within the meta-analysis had a decrease in HbA1c. Four of the studies showed no difference at all and one of the studies showed an increase of 0.2% in the patient's HbA1c. The next meta-analysis that was done looked at several types of diets and their effects on several different parameters including HbA1c. The study was done by Ajala et al. (2013) and it determined that the low carbohydrate, low GI, Mediterranean, and high protein diets all reduced HbA1c by between 0.12% and 0.5% compared to the control diets within each group. This paper also stated the significance of these numbers because a 0.5% decrease in HbA1c is comparable to the decrease that is achieved by pharmacotherapy. A critical review of carbohydrate restriction on diabetes management that was done by Feinman et al. (2015) showed that a low carbohydrate diet decreased HbA1c by an average of 0.68%. This study was particularly interesting because the low carbohydrate diet was done as a first line treatment for managing diabetes. Many of the other studies that have been looked at have not specified that the low carbohydrate diet was used as a first line treatment. In contrast to many of the studies that have already been examined, the study done by Tay et al.

(2015) showed that the HbA1c was decreased the same amount in both groups that were being studied. This study looked at a low carbohydrate diet group compared to a high carbohydrate diet group and found that there was no difference in HbA1c. It is important to note that there were 115 obese type two diabetics included in this study which lasted for 52 total weeks. The completion rate of both groups was the same. This study was similar to the meta-analysis study done by Kodama et al. (2009) that was done for the American Diabetes Association. Kodama et al. (2009) compared a high carbohydrate low fat diet with a low carbohydrate high fat diet. The analysis showed that there was no significant difference in the HbA1c outcomes, they were both comparable at the end of the studies that were included. This was also comparable to the study done by Jung and Choi (2017) which showed no difference in HbA1c between the low carbohydrate and high carbohydrate diet groups. Although these three studies showed no difference in the HbA1c at the end of the studies, it is still important to note the other benefits that were mentioned earlier of the low carbohydrate diet groups that can also benefit the health of type two diabetics.

Disadvantages of using diet management as first line treatment of type two diabetes mellitus. The most prominent disadvantage of using a low carbohydrate diet as first line treatment for T2DM is adherence. Feinman et al. (2015) found that adherence to the low carbohydrate diet was at least equal to if not better than other types of diets and it was also comparable to the adherence to pharmacologic interventions. They went on to say that they believe that the adherence to the low carbohydrate diet is due to the satiety and appetite suppression that come along with eating a diet with restricted carbohydrates. The satiety within this group is due to the increased protein and fat. One more thing that Feinman et al. (2015) noted was that the low carbohydrate diet group had unlimited access to food, but they had to

restrict their carbohydrate intake which they thought was easier to adhere to than other types of diets that had a strict reduction in calories leading to a lower adherence rate. In contrast to the study done by Feinman et al. (2015) that found adherence of the low carbohydrate diet group to be high, Huntriss et al. (2017) found the very low carbohydrate diet to be an unrealistic diet for type two diabetics to adhere to but found that the low carbohydrate diet was an achievable goal for these patients. Out of the six trials that tried the very low carbohydrate diet (<50 g per day) only one of the trials was completed with the average carbohydrate intake within the prescribed range, but all 12 studies that used the low carbohydrate diet (<130g per day) were able to complete the trial with average carbohydrates falling within the prescribed range. Although many of these studies showed that the low carbohydrate diet was beneficial for several health parameters, Kirk et al. (2008) discussed their concern about the sustainability of the results achieved by the low carbohydrate diet once the patient goes back to a higher carbohydrate intake. They also went on to say that until further research is done showing the safety and long term adherence, the low carbohydrate diet as a first line treatment for T2DM will remain a controversial topic.

Another disadvantage of using a low carbohydrate diet as a first line treatment of T2DM is that, as stated above in several studies, the low carbohydrate diet is not improving diabetic parameters significantly more than any other type of diet. Although a person would think that since carbohydrates are the major component of the diet that influences post prandial blood glucose (Kirk et al., 2008), decreasing the amount of carbohydrates would have a greater effect on lowering both blood glucose and HbA1c than other types of diets, that does not seem to be the case. The important thing seems to be a reduction in the patient's weight which can be obtained by any type of diet that causes a person to decrease their weight.

Metformin Pharmacotherapy Management of Type Two Diabetes Mellitus

Metformin is the prototype of the biguanides drug class and is considered the first line treatment for T2DM (Williams et al., 2014; Inzucchi et al., 2012). According to Bardal, Waechter, and Martin (2011) the biguanides have been used for hundreds of years to treat the symptoms that are associated with diabetes mellitus and they originally came from the French lilac plant. As already mentioned, the biguanides are antihyperglycemic drugs that lower basal and postprandial blood glucose levels and do this by decreasing the production of glucose in the liver and decreasing intestinal absorption of glucose in the distal small intestine as described by DynaMed Plus (2017e). Metformin has been used to treat diabetes mellitus by decreasing the patient's blood glucose levels, but because this drug does not stimulate the release of insulin, hypoglycemia is not a major concern according to Bardal et al. (2011). Now that the mechanism of action of metformin is understood, its effects on the type two diabetic can be further investigated.

Advantages of using metformin as first line treatment of type two diabetes mellitus. Although the primary parameter that is being examined throughout this study is HbA1c, it is again important to look at the other effects metformin may have on the type two diabetic patient. These other effects will be spread throughout this chapter rather than grouped because many of the studies included in the literature review examined only HbA1c.

According to the study done by Gonzalez-Ortiz et al. (2012) the participants in both the metformin glycinate and placebo group showed no significant change in weight at the completion of the research study. However, this study did show a greater than one percent drop in HbA1c in more than 60% ($P = 0.02$) of the participants at the completion of the study. This is found to be extremely significant because the study was only done over a period of two months.

This means that the originally measured erythrocytes were not completely out of circulation at the conclusion of the study. Although Gonzalez-Ortiz et al. (2012) found no difference in the body weight of patients taking metformin, Kashi, Mahrooz, Kianmehr, and Alizadeh (2016) found that patients taking metformin for three months had an average of 1.8% ($P < 0.001$) decrease in their BMI during that time. These same patients also saw a 4.1% ($P = 0.101$) rise in high density lipoprotein cholesterol and a 7.3% ($P < 0.001$) decrease in total cholesterol. Finally, they found that over a three-month period, the patients undergoing metformin therapy had a 0.65% ($p < 0.001$) decrease in HbA1c.

Because adherence is an important factor in effectively treating T2DM, it is important to look at the effects of adherence on a patient's treatment outcomes. The next study done by Nichols et al. (2016) took a unique approach to looking at the HbA1c changes of the patients within the study. This study was broken down into adherence groups and then each group's HbA1c change was calculated. Adherence below 50% showed no statistical difference in HbA1c, adherence between 50% and 79% had an average decrease of 0.45% ($P < 0.001$, 95% CI: 0.26 to 0.65) in HbA1c, and the adherence group of 80% or greater was associated with a decrease of 0.73% ($P < 0.001$, 95% CI: 0.55 to 0.9) in their HbA1c. Now that the positive effect of adherence on outcomes of treatment by metformin has been examined, another parameter to look at is what happens with metformin dosing if a person's sole treatment of T2DM is initiating pharmacologic treatment. Out of 176,556 newly diagnosed type two diabetics that started taking metformin, after four years on metformin 50% of these patients were in need of combination treatment because they had already increased their metformin to the maximum dose of 2500mg per day (Roumie et al., 2016).

Another interesting way to look at the effects of metformin on type two diabetics is to look at when the patient-initiated metformin therapy. Romanelli et al. (2015) studied two different groups that both initiated metformin therapy, one group-initiated therapy between zero and 20 days after diagnosis and the other group-initiated therapy between 466 and 1460 days after initial diagnosis of T2DM. During this study, the researchers found that the early initiation group had a 0.36% ($P < 0.001$, 95% CI: 0.27% to 0.44%) greater decrease in HbA1c and were also more likely to reach a HbA1c target value of less than 7%. Romanelli et al. (2015) also looked at the participant's BMI at the completion of the study and found that the early metformin initiation group had a 0.46 k/m^2 ($P < 0.001$, 95% CI: 0.29 k/m^2 to 0.64 k/m^2) greater decrease in BMI at the end of the study (which lasted between 325 and 329 days). Finally, this study found that for every additional month that metformin treatment was delayed, the patient had an average of 0.005% increase in their HbA1c. This shows that if a type two diabetic delays treatment without changing their lifestyle or diet, their HbA1c can rise very quickly.

The final study that was conducted compared the HbA1c of patients on the maximum dose of metformin (2500mg per day) to type two diabetics that were not treating their diabetes at all (Williams et al., 2014). This research found that the patients that were on the maximum dose of metformin had a 0.61% ($P < 0.001$) greater decrease in their HbA1c compared to the untreated group. It is important to note that these measurements of HbA1c were taken at least 120 days apart but anywhere from four to five months following the initial measurement. This study also broke the results down further into specific values according to ethnicity, but for the interest of the research at hand, the only value that will be mentioned here is the overall drop in HbA1c over all ethnicities.

Disadvantages of using metformin as first line treatment of type two diabetes mellitus. Although there are definite benefits of using metformin to treat T2DM (the major one being the decrease in HbA1c) it is still important to look at the opposing negative side of using metformin as treatment. The disadvantages of using metformin include, but are not limited to, possible hypoglycemic events, lactic acidosis, cost, and also the risk of not making any lifestyle changes to reverse the disease itself.

Metformin has a mechanism of action that decreases glucose production in the liver and because it is preventing the formation of glucose, this can lead to a low amount of glucose in the bloodstream or hypoglycemia (DynaMed Plus, 2017e). This side effect is not common, as described by DynaMed Plus (2017e), but there is still a risk that these episodes can occur. Even though this is listed as a disadvantage of using metformin as treatment for T2DM, this can also be caused by a patient missing or skipping a meal, excessively exercising, or drinking alcohol. This risk is, however, increased if the patient moves from solo metformin pharmacotherapy to combination therapy using metformin and another antihyperglycemic drug.

Another problem that may arise from using metformin as treatment for diabetes is lactic acidosis. According to Buse et al. (2016) the accumulation of metformin can stimulate increased production of lactate which can lead to a condition called lactic acidosis. To further explore this problem, it is important to note that metformin itself does not cause the lactic acidosis, but rather the use of metformin in a patient with other comorbidities such as heart failure, renal insufficiency, hypoxia, or sepsis can lead to the buildup of lactate and cause lactic acidosis to develop (DynaMed Plus, 2017e). The incidence of lactic acidosis developing in a patient taking metformin is 10.4 in every 100,000 patients per year (DynaMed Plus, 2017d). Although those

odds sound low, it is still important to be aware of because many diabetic patients have other comorbidities that accompany their T2DM.

The cost of metformin can be a burden on the patient as it can range between approximately $100 to $200 per month before insurance (Epocrates, 2012). If a patient does not have insurance, this prescription would be out of pocket each month which could potentially put a financial burden on the patient and his/her family. Conversely, if the patient does have insurance, this amount would more than likely be covered by insurance. When talking about 9.4% of the American population having T2DM, that is approximately 30 million people spending $100 to $200 dollars per month on metformin alone. Whether the money is coming from the patient or the insurance company, that is potentially 54 billion dollars being spent on metformin alone every year. (That being said, not every patient is on pharmacotherapy and of those patients that are, not every patient is on metformin. These calculations were only done to show the significant amount of money that could potentially be spent on metformin each year.)

The final disadvantage of using metformin as initial therapy for T2DM is treating a patient pharmacologically, but not actually treating the underlying cause of the T2DM. Let's look back and remember that obesity is one of the major risk factors for developing type two diabetes. This is because in obesity, there is fat that is deposited into the bloodstream and this fat increases insulin resistance in the body (DynaMed Plus, 2017a; DynaMed Plus, 2017f). According to DynaMed Plus (2017a) there is a Grade A recommendation for individualized dietary management for newly diagnosed type two diabetics. This is an important guideline to follow especially because as described by Roumie et al. (2016), once patients are put on metformin pharmacotherapy without initiating lifestyle changes (such as dietary management, physical activity, or diabetic education), these patients have a 50% chance of intensifying their

pharmacotherapy to combination therapy within four years. This shows that pharmacotherapy alone does not reverse the effects of T2DM. Finally, it is important to note that metformin is not the only drug used as an antihyperglycemic drug in patient's with T2DM. According to Qaseem, Barry, Humphrey, and Forciea (2017), most drugs used to treat T2DM lower the patient's HbA1c to very similar levels. Although metformin is often used as a first line pharmacotherapeutic agent for these patients, there are other drugs that are equally as effective at managing this disease.

The advantages and disadvantages of both a low carbohydrate diet and metformin as treatment for T2DM have now been thoroughly examined and compared. It is apparent that there is more than one way to treat type two diabetes and effectively lower HbA1c. Both methods of treatment were found to be effective, so when treating these patients, providers really need to compare the advantages and disadvantages to each individual patient to determine what would work best for him or her.

Discussion

Throughout the reading and research that has been done for this project, it has become very clear that there is more than one effective way to treat newly diagnosed T2DM. The low carbohydrate diet treatment option helps lower HbA1c, raise high density lipoprotein cholesterol, lower triglycerides, lower body weight, and lower fasting and post prandial blood glucose levels. The metformin pharmacotherapy treatment option is efficient at lowering HbA1c and may help lower a patient's BMI and total cholesterol and raise their high density lipoprotein cholesterol.

In newly diagnosed type two diabetics presenting for initial treatment, does a low carbohydrate diet or metformin have a greater effect on lowering HbA1c?

Through the above research, it was found that using a low carbohydrate diet almost always decreased the patient's HbA1c, but in one study within the meta-analysis done by Huntriss et al. (2017) there was a 0.2% increase. Huntriss et al. (2017) noted that there was one big limitation within their studies and that was the lack of blinding the participants and personnel conducting the studies. In all other studies reviewed within this project, there was between a 0.2% decrease (Huntriss et al., 2017) and a 2.2% decrease (Kirk et al., 2008) in HbA1c. Metformin on the other hand had a 0.45% ($P < 0.001$, 95% CI: 0.26 to 0.65) decrease in HbA1c (Nichols et al., 2016) in a group of patients that had an adherence rate of 50% to 79% up to a greater than one percent decrease in HbA1c as expressed by Gonzalez-Ortiz et al. (2012). It is also important to note that within the research reviewed, there were no studies that showed an increase in HbA1c in patients taking metformin.

A problem that was encountered with this research was that the amount of studies that were done on the efficacy of metformin in lowering a newly diagnosed type two diabetics HbA1c within the past ten years were limited. It is hypothesized that because metformin has

been around and used for diabetic treatment for such a long time that the efficacy is already proven and accepted by the medical community. The studies that were found seemed to have another element to them which made them pertinent studies to today's medical practices.

What are the advantages of a low carbohydrate on lowering HbA1c?

The low carbohydrate diet can be beneficial to all type two diabetic patients because it can help these patients improve health parameters including weight, high density lipoprotein cholesterol, triglycerides, and HbA1c. A low carbohydrate diet effectively decreases BMI according to Tay et al. (2015), Feinman et al. (2015), Kirk et al. (2008), and Huntriss et al. (2017). All of these studies found that a low carbohydrate diet decreased a patient's body weight and therefore improved their BMI. Although these studies all showed a decrease in body weight, both Kirk et al. (2008) and Huntriss et al. (2017) found that there was no statistical difference between the weight loss from a low carbohydrate diet versus the other types of diets that were studied. This is significant to the current research because the main factor that was affecting body weight was that the patient was adhering to a diet. This means that there may be more leeway to choose what type of diet would work best with each individual patient rather than automatically going straight to the low carbohydrate diet.

The low carbohydrate diet did, however, cause a rise in high density lipoprotein cholesterol exhibited by Ajala et al. (2013) which showed there was a ten percent increase in high density lipoprotein cholesterol in patients that adhered to a low carbohydrate diet for type two diabetic treatment. An even more significant result of the low carbohydrate diet is the decrease in patient's triglycerides. Feinman et al. (2015), Kirk et al. (2008), Kodama et al. (2009), and Jung and Choi (2017) all found that there was a significant decrease in triglycerides in the patient groups that implemented a low carbohydrate diet as treatment for their type two

diabetes. The decrease in triglycerides ranged from 13.4% to 22%. These changes in cholesterol are important to the diabetic patient because by lowering their triglycerides and raising their high density lipoprotein cholesterol, this improves their overall cardiovascular health and can further reduce their risk of myocardial infarction which, as mentioned earlier, is increased in a type two diabetic patient (DynaMed Plus, 2017g).

Finally, let's examine the benefits that the low carbohydrate diet has on HbA1c in the type two diabetic patient. Although all of the studies showed a decrease in HbA1c, many of the studies showed no significant difference between the HbA1c effects from the low carbohydrate diet versus the other types of diets studied. Ajala et al. (2013) found that the low carbohydrate, low GI, Mediterranean, and high protein diets all reduced HbA1c approximately the same amount similar to Tay et al. (2015), Kodama et al. (2009), and Jung and Choi (2017) who all found that the low carbohydrate and high carbohydrate diets had no difference in the amount that they decreased HbA1c. There was, however, one study done by Yamada et al. (2014) that found that the calorie restricted diet group had no change in their HbA1c, but the low carbohydrate diet group had a decrease of 0.6% ($P = 0.03$) in their HbA1c. This evidence causes a person to think that the most important factor in reducing HbA1c is not the type of diet that the patient is on, but the actual adherence to a diet with specific guidelines other than just the reduction of calories.

What are the disadvantages of a low carbohydrate diet on lowering HbA1c?

There were several studies done on the effects of a low carbohydrate diet on a type two diabetics HbA1c, but unfortunately, it was not specified within many of these studies whether the low carbohydrate diet was a solo treatment being used for treating the patient or whether it was added on as a combination therapy with a pharmacologic treatment. Because of this, it is not

completely definitive that the decrease in HbA1c that was seen was solely due to the patient's change in diet.

Many of the studies examining the effects of a low carbohydrate diet on HbA1c did not specify what they meant by low carbohydrate. The studies done by Feinman et al. (2015) and Huntriss et al. (2017) did specify that a low carbohydrate diet was defined as less than 130 g/d which is less than 26% of a 2000 kcal/d diet. Since the other studies did not specify their definition of a low carbohydrate diet, it is not clear that the patients were consuming the same amount of carbohydrates as the above-mentioned studies. This could skew the results of the studies depending on if the patients were consuming more or less carbohydrates. If they were consuming less carbohydrates than the amount defined above, this could make the diet difficult for patients to adhere to and result in lower adherence rates which could ultimately result in failed treatment.

That leads us into the last disadvantage which is adherence. If a treatment plan is not adhered to by the patient, it has zero chance of being successful. Not every patient is going to be willing to adhere to a low carbohydrate diet in order to lower their HbA1c. Only the highly motivated and determined patient's will be willing to go down this road of treatment and providers need to be able to determine (with the patient) whether this is a reasonable option for them. If the patient is not willing to do this treatment option, then other types of treatments will be more beneficial to those particular patients.

What are the advantages of metformin pharmacotherapy on lowering HbA1c?

The most important advantage of using metformin pharmacotherapy is the effect it has on decreasing HbA1c. The studies show that a patient taking metformin has a decrease in HbA1c ranging from 0.45% to greater than 1% (Nichols et al., 2016; Gonzalez-Ortiz et al. 2012). This

decrease in HbA1c is important because it reduces the patient's risk of myocardial infarction, neuropathy, nephropathy, and retinopathy according to DynaMed Plus (2017b). It is important to note that Gregory A. Nichols who conducted the study done by Nichols et al. (2016) was receiving funding from various pharmaceutical companies for other unrelated research projects at the same time that this study was being conducted.

Initiating metformin therapy at the onset of T2DM diagnosis is very important to a patient's overall health. Romanelli et al. (2015) found that patients that started taking metformin within approximately three weeks of their diagnosis had a significantly higher chance of reaching the goal range of less than 7% in HbA1c. This group also had a 0.36% greater decrease in HbA1c during the study. Finally, this study found that for each month that metformin pharmacotherapy was delayed, the patient would have a 0.005% increase in HbA1c.

Another important benefit of metformin pharmacotherapy in the type two diabetic is the more adherent the patient is to the prescribed therapy, the greater decrease they will see in their HbA1c. Nichols et al. (2016) found that in the group that had a lower than 50% adherence to their prescribed treatment, there was no change in HbA1c. The group that had between 50% and 79% adherence saw a decrease in HbA1c of approximately 0.45% ($P < 0.001$, 95% CI: 0.26 to 0.65) and the group with 80% or greater adherence to their metformin therapy saw a decrease of about 0.73% ($P < 0.001$, 95% CI: 0.55 to 0.9) in their HbA1c. This study shows the importance of not only starting metformin pharmacotherapy, but the importance of taking it as prescribed. The importance of adherence is something that must be explained to the patient along with why the decrease in HbA1c is so important. Although providers understand the need to get the patient's HbA1c within target range, it is not common knowledge and must be explained in lay

terms to these type two diabetic patients if they are to be expected to adhere to their metformin pharmacotherapy.

What are the disadvantages of metformin pharmacotherapy on lowering HbA1c?

Metformin has been a first line treatment for T2DM for many years and has been shown to effectively lower HbA1c, but it is still important to look at the possible disadvantages of this specific pharmacotherapy treatment. The disadvantages that have been found throughout this project have been possible negative side effects, the cost, and the fact that metformin is not the only diabetic medication that effectively lowers HbA1c.

With almost any type of pharmacotherapy that can be initiated, there are risks of side effects. Also, every patient reacts to different medications in different ways, so it is important to consider each of the possible side effects with each patient so that they can watch for signs. The main two serious side effects that should be watched for with metformin are hypoglycemia and lactic acidosis (Bardal et al., 2011; Buse et al., 2016).

The cost of metformin can add up quickly for a type two diabetic patient. This cost sometimes is the responsibility of the patient if they don't have good (or any) prescription insurance coverage or it is paid for by insurance companies. Either way, this can be a huge expense which could be up to 54 billion dollars per year being spent on T2DM metformin pharmacotherapy in the United States alone (Epocrates, 2012). This is a huge amount of money that could potentially be spent if every type two diabetic patient in the United States initiated metformin therapy. If this condition had no other treatment options, the amount of money would not be quite so alarming, but knowing that there are other treatment options that could avoid the expense of this pharmacotherapy, this seems like an unnecessary expense.

Finally, Qaseem et al. (2017) found that most diabetic drugs were shown to lower HbA1c to approximately the same level. This means that there are different pharmacotherapy options available that can decrease HbA1c and possibly improve other health parameters as well. This is another topic that could be researched in depth to determine the most beneficial pharmacotherapy treatment for each individual type two diabetic patient.

How the Research Applies to Clinical Practice

Almost one tenth of the population of the United States of America is currently diagnosed with T2DM according to the American Diabetes Association (2017). There are several factors that contribute to the likelihood of an individual developing type two diabetes including obesity, metabolic syndrome, polycystic ovary syndrome, and family history (DynaMed Plus, 2017a). Throughout the research done for this project, it has become evident that there is more than one way to treat T2DM. The two treatments that have been compared in depth are metformin pharmacotherapy and a low carbohydrate diet.

Seeing that obesity, which is a preventable and reversible factor, is one of the biggest risk factors for T2DM it seems reasonable that using a low carbohydrate diet would be beneficial in treating T2DM. With a low carbohydrate diet, a patient is able to lower their body weight and BMI, raise their high density lipoprotein cholesterol, lower their triglycerides, and decrease their HbA1c. The problem is that not every patient is going to be ready and willing to adhere to a strict diet to treat their type two diabetes. This is especially true for patients who know how effective oral medications are at treating diabetes. This is where education comes in. It is important to educate these patients and even involve the registered dietician and diabetic educator so that the patient is able to make a decision about their treatment having all the facts that are necessary. The low carbohydrate diet is effective at treating T2DM only in the patients who are ready and willing to adhere to the diet and make a lifestyle change to improve their health without pharmacotherapy.

Metformin, on the other hand, has been used as a first line treatment for T2DM for centuries (Bardal et al., 2011). It has been proven to be effective and is an oral drug that is not difficult to add into a person's every day routine. The problem, however, is if a patient does not

make any lifestyle changes, their diabetes is going to progress and they will continue to increase their dosage of metformin and eventually move to combination therapy which will eventually lead to the need for insulin. It is believed that even if a patient begins metformin pharmacotherapy immediately at diagnosis of T2DM, there must be consultation with a diabetic educator and registered dietician with frequent follow ups. These patients must be educated on what diabetes mellitus can do to their bodies and the importance of also making lifestyle changes to avoid the major complications that may arise due to T2DM.

It was not found that either the low carbohydrate diet or metformin pharmacotherapy was more effective. They were both proven to be effective at lowering a patient's HbA1c, but the main thing that was found was that each patient is different and a treatment that fits well in one patient's life may not be reasonable in another patient's life. Each patient that is diagnosed with T2DM must be educated on the treatment options and provided the support they need to both decide on a treatment option and adhere to it. There are many options, but each patient is unique and needs to be provided with understanding and support of their situation to allow them to be successful in treating their T2DM.

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