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Independent Study

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Abstract

Type 2 diabetes is a progressive disease involving insulin resistance and decline in Beta-cell function. As type two diabetes progresses, patients eventually need the use of exogenous insulin. There are many negative outcomes with insulin use compared to other treatments. Dietary carbohydrates exert a much higher response on glucose levels than proteins and fats and the current thought is by decreasing carbohydrates, hyperglycemia and the insulin response would also be reduced. The aim of this review is to determine if compliance with a low carbohydrate diet delays the need for more antidiabetic medications and eventual need for insulin therapy. A case profile is presented to show how a patient could benefit from a low carbohydrate diet as part of the management of type 2 diabetes.

The patient is a 65 year asymptomatic male with type two diabetes with an HbA1c of 9.4%. The patient was treated with an increased dose of metformin and the addition of Glipizide 2.5mg. A review of the literature was conducted which included 10 journal articles. Eight out of the ten articles showed that participants restricting carbohydrates to 45% or less of their daily intake had improved glycemic control demonstrated by greater decreases in their HbA1c and reduction of antidiabetic medications. With these results, one could hypothesize that adherence to a low carbohydrate diet delays the progression of disease and eventual need for insulin.

Background

Type 2 diabetes is a progressive disease involving insulin resistance and decline in Beta-cell function. In pre-diabetes, beta cells initially secrete increased amounts of insulin to combat insulin resistance, creating a state of hyperinsulinemia. Over time, beta cells lose function and are unable to secrete adequate insulin and blood glucose levels begin to rise. By the time diabetes is diagnosed, insulin producing beta cells have lost a significant amount of their function. As individuals progress through the disease, their beta cells continue to decline in function and patients eventually need to use injectable insulin to control blood sugars.

Insulin therapy involves patients giving themselves daily injections and is associated with an increased risk for complications compared to other treatments. A recent study following 84,622 primary care patients with type 2 diabetes from 2000 to 2010 showed that those on insulin therapy die at a significantly higher rate than those using other treatments (Currie, Poole, Evans, Peters, & Morgan, 2013, p. 668). The study compared metformin monotherapy, Sulfonylurea monotherapy, insulin monotherapy, duel therapy with metformin plus a Sulfonylurea, and metformin plus insulin therapy. These groups were compared to determine risk associated with vascular events and death. Metformin monotherapy was used as the reference as it had the lowest number of negative outcomes. The study showed that those using insulin had 1.95 times more myocardial infarctions, 1.43 times more strokes, 1.74 times more cardiac complications, 3.5 times more renal complications, and 2.2 times more deaths when compared to those taking metformin (Currie et al., 2013, p. 668). Insulin is also associated with hypoglycemia which can be fatal if not corrected. It’s very important to preserve beta cell function and prevent the need for insulins to avoid the increased risks for diabetic complications, side effects of hypoglycemia, and difficulty of use.

The purpose of this paper is to determine if compliance to a low carbohydrate diet slows the progression of type 2 diabetes and the eventual need for insulin therapy. Currently the American Diabetics Association (ADA) does not recommend any specific diet for diabetic patients, only a decrease in caloric intake (Dunphy et al., 2015, p. 893). However, evidence has shown that carbohydrates elicit a much greater increase in post prandial blood glucose than protein or fat (Tay et al., 2014, p. 2909). Insulin is secreted in response to increased glucose levels. This relationship supports the hypothesis that increased consumption of carbohydrates is linked to continued high levels of glucose and insulin, which may exacerbate or cause an insulin resistant state (Feinman & Volek, 2008, p. 256). It is hypothesized that by reducing dietary carbohydrates, glucose and insulin levels will return to a normal level (Feinman & Volek, 2008, p. 256).

Case Report

The patient is a 65 year old male who presented to the clinic for follow up of his type 2 diabetes. He had recently seen a diabetic educator 2 weeks prior, who had advised him that his blood sugars were running too high and referred him to a provider for further management. He reports that he was diagnosed with type 2 diabetes two years ago. He records his fasting blood sugar each morning. Most recently these were 135 and 142 which is typical for him. To control his diabetes he has been trying to count his daily carbohydrate intake and has been attempting to consume less of them. He reported that he was trying to exercise a few times a week for 30 minutes. He stated that he is feeling well and he denies any symptoms such as vision changes, polydipsia, polyuria, polyphagia, weight loss, peripheral neuropathy, skin color changes, unhealed wounds, chest pain or shortness of breath.

The patient has a past medical history of type two diabetes, hypertension, hyperlipidemia, coronary artery disease, and lower extremity edema. Surgical history includes cardiac

catheterization with stent placement. He has an extensive family history of type two diabetes, including his father and both of his brothers. He is currently taking metformin 500 mg twice a day, Plavix 75mg daily, aspirin 81 mg daily, Lasix 20mg daily, Lisinopril 20mg daily, atorvastatin 20mg daily, and a daily multivitamin.

The patient's physical exam was unremarkable. He was alert and orientated, had a regular heart rate and rhythm, S1 and S2 heart sounds present on auscultation with no extra sounds, peripheral pulses were palpable 2+, extremities were warm, no edema present, skin was appropriate for race. He had no JVD distension, carotid pulses were equal, no bruits to carotid, aortic, renal, iliac, and femoral arteries. His respirations were equal, non-labored, and clear upon auscultation. His sensation to his feet was intact to soft touch, skin was intact and color appropriate for race, no edema with even hair distribution. His vitals were as follows: BP 122/64, HR 64, and BMI 25.

The patient had the following labs collected, LFT's, fasting lipid profile, urinalysis, BMP, CBC, and HbA1c. The patients CBC, and LFT's were unremarkable. His fasting lipid profile was unremarkable with the exception of HDL being low at 38. His BMP was unremarkable with the exception of a serum glucose of 151, estimated GFR of 49 and creatinine level of 1.3. His urinalysis showed microalbuminuria. His HbA1c was elevated at 9.4%. The patient's current diagnosis is type 2 diabetes uncontrolled without complications.

The plan for this patient was to make changes to obtain an A1C goal of below 7 per ADA recommendations. His Metformin dose was increased to 1000 mg two times a day over a two week span. The patient was also started on a low dose sulfonylurea (glipizide) 2.5 mg daily. He was educated on potential side effects and to watch for symptoms of hypoglycemia with this medication. He was educated on importance of diet, exercise and weight loss to obtain adequate

glycemic control. It was recommended that he follow up in 1 week to assess for any hypoglycemia with these medication changes. If he is tolerating his medications, the plan is to follow up in three months to check his HbA1c.

Literature Review

To determine if the progression of this patient's diabetes and his potential need for insulin therapy could be slowed by adhering to a low carbohydrate diet, a literature review was performed using the University of North Dakota's online databases through the Harley E. French Library of Health Sciences. Due to a lack of evidence specifically focused on this question, it was necessary to look at related studies regarding diabetes and diet management and infer an answer based on the results and current findings of these studies.

The first piece of evidence was a systematic review by Kirk et al. (2008) which supported that adherence to a low carbohydrate diet (LCD) improves glycemic control. This review defined LCD as carbohydrate intake of 45% or less. Eleven studies were included evaluating HbA1c outcomes between LCDs and low calorie high carbohydrate diets (HCD). In 7 studies, HbA1C was significantly lowered from baseline ranging from 0.5%-2.2% more in the LCD participants compared to the HCD participants (Kirk et al., 2008, p. 94). The studies included in this review ranged in length from 2-26 weeks. The number of participants in these studies was small ranging from 8-52. The results of this review suggest that the short term use of carbohydrate restricted diets improves glycemic control compared to unrestricted carbohydrate low calorie diets (Kirk et al., 2008, p. 99). The evidence in this review is limited by the small sample sizes and the short duration of the studies. Larger and longer term studies need to be done to confirm long term glycemic control (Kirk et al., 2008, p. 99).

In contrast, the second systematic review by Van Wyk et al. (2015) did not support that LCDs improved HgA1c compared to HCDs. This review included 12 randomized control trials. Only one study in the review showed a significant reduction in HbA1c between low carbohydrate versus high carbohydrate diet groups. In the remaining studies, adherence to the prescribed diet worsened as time went on, a significant confounder. In one study, the mean intake of carbohydrates in the LCD group was 154 grams which was far from the prescribed less than 30 gram goal (Van Wyk et al., 2015, p. 151). The review also noted the carbohydrate intake between the two groups in some of the studies was much smaller than intended. One study had only 1 gram difference between groups for the average daily intake (Van Wyk et al., 2015, p. 151). The review also discussed three studies in which antidiabetic medications were decreased at a higher rate in the LCD than the HCD. One study showed that 95.2% of those on the LCD stopped or reduced antidiabetic medication compared with 62% in the HCD (Van Wyk et al., 2015, p. 151). The review concluded that the LCD did not show better glycemic control than HCDs. These results need to be taken with caution as adherence to the LCD was low and there was an increased reduction in antidiabetic medications in LCD participants (Van Wyk et al., 2015, p. 156).

The third piece of evidence by Saslow et al. (2014) supported that low carbohydrate diets improve glycemic control in type two diabetics. This randomized control trial compared the ADA recommended moderate carbohydrate calorie restricted (MCCR) diet to a low carbohydrate ketogenic diet (LCKD). Participants attended 13 one hour sessions with a dietician focusing on the prescribed diet. The MCCR participants had calories restricted to 500 calories below their metabolic needs and were to consume 50% of their diet from carbohydrates. The LCKD group had no restriction on calories but were restricted to 50 grams of net carbohydrates. Food diaries

were maintained in each treatment arm. HbA1c results were drawn at the beginning of the study and again at 3 months in each treatment arm. There were a total of 34 participants enrolled and randomly assigned with 18 in the MCCR diet arm and 16 in LCKD diet arm. On average HbA1C did not change from baseline in the MCCR group and changed -0.6% from baseline in the LCKD group (Saslow et al., 2014, p. 5). Every individual in the LCKD group had an improvement in HbA1c with 56% of participants having greater than a -0.5% reduction (Saslow et al., 2014, p. 5). In the MCCR group only 72% had improvement in HbA1c and only 22% had a -0.5% reduction (Saslow et al., 2014, p. 6). Additionally 44% of those in the LCKD group discontinued one or more diabetes medications compared to 11% in the MCCR group (Saslow et al., 2014, p. 6). The study concludes that a LCKD may be more effective for glycemic control for type two diabetics that the ADA recommended MCCR diet (Saslow et al., 2014, p. 1027).

The fourth piece of evidence by Elhayany et al. (2010) also supported that low carbohydrate diets improve glycemic control. The study was a randomized control trial comparing a low carbohydrate Mediterranean diet (LCMD) to the ADA diet over a 1 year time period. The composition of each diet were as follows: ADA diet 50-55% from carbohydrates, 30% fats and 20% protein versus the low carbohydrate Mediterranean diet 35% from carbohydrates, 45% from fats- high in monounsaturated fat content and 15-20% proteins (Elhayany et al., 2010, p. 205). Participants with type two diabetes were randomly assigned with 89 in the ADA diet and 85 to the LCMD. These diets were iso-caloric. Participants met with a dietician every two weeks during the study. Daily food logs were kept and reviewed during each visit. Both diets resulted in significant reductions in HgA1c compared to baseline but the LCMD had a greater reduction: 8.3% to 6.7% in the ADA diet and 8.3% to 6.3% in the LCMD (Elhayany et al., 2010, p. 207). The study concluded both these diets improved glycemic control but the more carbohydrate

restricted LCMD had more significant improvements in HbA1c. Both of these diets in this study restricted carbohydrates and showed significant reductions in HbA1c strengthening the idea that carbohydrate restriction improves glycemic control.

The fifth piece of evidence by Mayer et al. (2014) also supported improved glycemic control in low carbohydrate diets. This study was a randomized control trial that analyzed a low fat diet vs low carbohydrate diet in type 2 diabetics. The study contained 46 participants that were randomized to either the low carbohydrate diet which restricted carbohydrates to less than 20g with no calorie restrictions or a low fat diet which restricted fat to 30% and saturated fat to 10% and calories 500-1000 below metabolic needs. The low carbohydrate arm included 22 participants and the low fat arm included 24 participants. The low carbohydrate diet arm had a greater reduction in HbA1c than the low fat diet after completion of the 48 week study. The initial mean baseline HbA1c in the low carbohydrate group was 7.6% which was reduced to 6.9% at study completion (Mayer et al., 2014, p. 3). In the low fat group initial mean HbA1c was 7.6% and after study completion was 7.7% (Mayer et al., 2014, p. 3). The difference in HbA1c was significant between the two groups with a mean change of -0.8% (95% CI= -1.6, -.02; P=0.045) (Mayer et al., 2014, p. 3). Antidiabetic medications were also decreased at a higher percentage in the LCD arm with 70.6% of participants reducing them by 50% compared to 30.4% of participant in the low fat group (Mayer et al., 2014, p. 3). This study concluded that low carbohydrate diets may have a greater effect on reducing HbA1c and antidiabetic medication in type 2 diabetics than low fat calorie restricted diets (Mayer et al., 2014, p. 4).

The sixth piece of evidence by Westman et al. (2008) also supported that low carbohydrate diets improve glycemic control in type two diabetics. This randomized control trial compared a low carbohydrate ketogenic diet (LCKD) to a low glycemic index diet (LGID). The LGID

consisted of 55% of daily intake from carbohydrates with the energy intake to be 500 calories below the individual's metabolic needs. The LCKD group was to restrict carbohydrates to 20g or less without restriction on total caloric intake. Participants were randomized to either group and after dropout was accounted for, 21 were included in the LCKD arm and 29 in the LGID arm. HbA1c was drawn at baseline, 12 weeks, and 24 weeks. The LCKD group had a significant reduction in HbA1c on average compared to the LGID group from baseline to week 24 with mean changes of -1.5% in the LCKD arm compared to -0.5% in the LGID arm (Westman, Yancy, Mavropoulos, Marquart, & McDuffie, 2008, p. 4). Antidiabetic medications were also decreased at a higher rate in the LCKD group. Medications were reduced or eliminated in 20 of 21 (95.2%) participants in the LCKD group compared to 18 of 29 (62.1%) of LGID participants (Westman et al., 2008, p. 4). This study supported that carbohydrate restricted diets improve glycemic control and reduce antidiabetic medications in type two diabetics and may play an important role in reversing type 2 diabetes (Westman et al., 2008, p. 8).

The seventh piece of evidence by Tay et al. (2014) also supported that low carbohydrate diets improve glycemic control in type 2 diabetics. This randomized control trial compared a very low carbohydrate, low saturated fat diet (VLCD) to an energy matched HCD in the management of type 2 diabetes. The study was a randomized trial which included participants that were type 2 diabetics. The VLCD restricted carbohydrates to less than 50 grams a day and had a goal of 28% of energy from proteins 58% from fats of which 35% were monounsaturated fats and 13% were polyunsaturated fats. The high carbohydrate diet included 53% energy from carbohydrates 17% from protein and 30% from fat, restricting saturated fat to 10%. The low carbohydrate arm consisted of 46 participants and in the high carbohydrate arm 47 participants. Calories were restricted to 500-1000 below each participant's metabolic needs. Participants met with a dietician

every other week for the first 12 weeks and then monthly for the rest of the study. Daily logs were kept of dietary nutrients and energy consumption was similar between the two groups. Both groups had significant drops in HbA1c compared to baseline, but the VLCD group had an average of -0.7% more than the high carbohydrate group (Tay et al., 2014, p. 2913). Antidiabetic medications were also decreased in both groups, but again more in the low carbohydrate group. After the 24 week study, the VLCD group experienced double the reduction in antidiabetic medications compared to the HCD with more participants achieving a reduction of 20% or more (Tay et al., 2014, p. 2914). This study supports that low carbohydrate diets improve glycemic control and reduce diabetes medication requirements among type two diabetics (Tay et al., 2014, p. 2915).

The eighth piece of evidence was another study by Tay et al. (2015) with the same design as the previous study. The goal of this study was to determine if a VLCD could sustain improved glycemic control over 52 weeks compared to a HC calorie restricted diet. Participants with type two diabetes were randomly assigned to either a hypocaloric LC diet or VLCD exactly the same as the previous trial. The HCD had 37 participants complete the study and 41 in the VLCD. Both groups had similar reductions in HbA1c at the end of the study with both arms averaging a -1% decrease from baseline (Tay et al., 2015, p. 780). The VLCD arm had a significant reduction in diabetic medications compared to the HCD arm. In the VLCD arm 52% of the participants decreased there diabetic medications by 20% or more compared to 22% of the participants in the HCD arm (Tay et al., 2015, p. 780). Reported dietary intakes were consistent for energy between the two groups. This study shows that low carbohydrate diets over the long term decrease the need for antidiabetic medications thus improving glycemic control greater than diets without restrictions on carbohydrates (Tay et al., 2015, p. 788).

The ninth article by Davis et al. (2009) did not support that low carbohydrate diets improve glycemic control. The study was a yearlong RCT comparing the effects of a low carbohydrate diet vs a low fat diet on weight and glycemic control. HbA1c levels were drawn at baseline, at three months, six months, and after 1 year. This trial involved 105 participants with type 2 diabetes who were randomized to each treatment arm with 55 participants in the low carbohydrate diet arm and 50 participants in the low fat diet arm. The low carbohydrate diet was based on the Atkins diet and carbohydrates were restricted to 20-25 grams. The low fat diet put a limit on fat to less than 25% of energy needs. Each participant received a booklet about foods high in fat or carbohydrates and received 45 minutes of dietary instructions from a dietician. Participant also followed up with a nutritionist for 30 minutes every two months. At the three month mark HbA1c was significantly lower in the low carbohydrate group with participants on average showing a -0.64% decrease compared to the low fat group -0.26% decrease (Davis et al., 2009 , p. 1148). However, this difference was not sustained and at the one year mark there was no significant difference in HbA1c from baseline between the two groups. Food logs indicated that after the first three months adherence to prescribed diets diminished in both arms. At the end of the study neither group had a significant drop in HbA1c. The participants in this study consisted mostly of African Americans and Hispanics whom consumed high carbohydrate high fat diets at baseline (Davis et al., 2009 , p. 1151). This study showed that the short term improved glycemic control in HCD's was not sustainable over a yearlong study.

The tenth article by Hussain et al. (2012) showed that LCD's improve glycemic control and decreases the need for antidiabetic medications. This study tested the effects of a low calorie vs a low carbohydrate ketogenic diet (LCKD) diet in type 2 diabetes in regards to glycemic control over 24 weeks. This trial included 102 participants with type 2 diabetes and allowed them to

choose which diet intervention they wanted to participate in. The LCKD group consisted of 78 participants and low calorie group 24 participants. The participants were educated on their chosen diet and followed up every other week for additional dietary and medication counseling (Hussain et al., 2012, p. 1018). The LCKD diet had a goal of less than 20g of daily carbohydrates and the low calorie group just had a restriction on calories of 2200. Diabetic medications in the LCKD were cut in half at initiation of the study and modified based on twice daily fasting blood sugars (Hussain et al., 2012, p. 1018). The LCKD participants had an average baseline HbA1c of 7.8% and after the 24 week intervention had a significant decrease to an average of 6.2% (Hussain et al., 2012, p. 1018). The low calorie diet had an average baseline level of 8.2% and after the intervention decreased to 7.7% (Hussain et al., 2012, p. 1018). These results show that the LCKD seems to have a much greater effect on reducing HbA1c than calorie restricted high carb diets (Hussain et al., 2012, p. 1021).

In conclusion, the literature review shows that carbohydrate restriction is an important dietary intervention for glycemic control. In 8 out of the 10 articles reviewed there were significant decreases in HbA1c and antidiabetic medications. The two articles that did not support this showed a lack of adherence of the diet. When adherence is maintained the evidence shows improved glycemic control and reduction in need for antidiabetic medications. In addition, the low carbohydrate diets showed these improvements in 4 studies despite lack of calorie restriction demonstrating that carbohydrate restriction is an independent predictor of improved glycemic control. One may also question if the low carbohydrate diet was correlated with increased weight loss, which is very beneficial for glycemic control. The studies in this review did not reflect this, as weight loss was similar between LCDs and HCDs.

There are limitations to the evidence from the studies reviewed. First, there is significant risk for recall bias and error when people are self-reporting food intake. They may have poor recall of what they consumed or they may be simply falsifying data to comply with diet rules. The evidence is also limited by the small number of participants and length of studies. There were no studies beyond one year making long term efficacy difficult to extrapolate. One of the yearlong studies by Davis et al. (2009) showed a lack of dietary adherence indicating long term adherence may be very difficult. The evidence reviewed has numerous limitations but all the studies showed improvement in glycemic control and reduction of diabetic medications when low carbohydrate diets were followed.

Based on these findings, it cannot be concluded that low carbohydrate diets prevent the eventual need for insulin therapy but research demonstrates they are effective short term in improving glycemic control and reducing need for diabetic medication. However, the evidence is supportive of the hypothesis that if a LCD can be maintained long term, this could lead to a reduction in insulin therapy. Further studies will be needed to assess the long term benefits and whether this significantly decreases the likelihood of insulin therapy. Based on the evidence, I would recommend that my patient follow a low carbohydrate diet and would share the evidence demonstrating decreases in HgA1c, medication dose reductions, and reduced need for additional medications. With adherence to a low carbohydrate diet, the patient in the presented case would likely be able to discontinue his glipizide while also improving his glycemic control.

Take Home Points

- Type 2 Diabetes is a disease characterized by insulin resistance with progressive loss of beta-cell function resulting in the need for insulin therapy which is associated with more complications than other treatments.

- Current recommendations from the ADA includes decreased caloric intake and weight loss but do not include a low-carbohydrate diet despite evidence that adherence with low-carbohydrate diets improve glycemic control.
- Current evidence demonstrates that low-carbohydrate diets decrease HgA1c and decrease the need for diabetic medications in short-term studies.
- Longer term studies are needed to address the ability of low carb diets to decrease the need for insulin therapy.
- Further studies need to be done to determine the degree of carbohydrate restriction to obtain the most benefit.

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