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Strict Glycemic Control in Adults with Type 2 Diabetes and Risk of Infection

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PERMISSION

Title	Strict Glycemic Control in Adults with Type 2 Diabetes and Risk of Infection
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Abstract

Diabetes is one of the most commonly diagnosed chronic diseases in medicine. According to the Center for Disease Control (2020) more than 10% of the United States population is diagnosed with diabetes, and it is the seventh leading cause of death. The most common complications related to diabetes include heart disease, stroke, blindness, eye problems, kidney disease, nerve damage, amputations, and wound complications (CDC, 2020). Diabetes can also be associated with an increased risk for infection-related mortality (Li & McDermott, 2016). This literature review will focus on the potential that strict management of diabetes can decrease the risk of infection for this population. It is well documented that diabetics are at a higher risk for infection due to immunosuppression. However, it is not well studied within how strict of measures we should set a goal for our patients with the aim to decrease the risk for infection. Li & McDermott (2016) stated that in 2001 the cost of diabetic wounds cost 10.9 billion dollars and that the length of stay for diabetics with infections is on average 6 days in comparison to 3.4 days for non-diabetics with infection. Hospitals are always looking for ways to budget better, reduce cost, and reduce length of stay. These statistics alone stand out as reasons to do further research on the prevention of infection in type 2 diabetics.

Search Parameters

Research was done by using the databases CINAHL and PubMed. Keywords included “glycosylated hemoglobin”, “type 2 diabetes”, “HbA1c”, “infection”, “cellulitis” and publication dates were set between 2015 to 2020. Recommendations from the Center for Disease Control, the American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) were reviewed as well. Certain articles were excluded from review if they were focused on independent variables that could affect infection or hemoglobin A1c, any

non-English articles, articles that included only type 1 diabetes, and articles that did not use hemoglobin A1c as the compared variable.

Background

Diabetes mellitus (DM) largely infiltrates our healthcare system and it is only projected to expand further. There are currently 26.9 million people in the US who are diagnosed with diabetes and it is expected that there are approximately 7.3 million people who are yet undiagnosed (CDC, 2020). It is well studied and accepted in the literature that there is a strong association between glycemic blood levels and the risk of developing diabetic complications such as infection. The increased risk for infection can be attributed to elevated glucose content in bodily fluids, which provides an ideal breeding ground for bacterial proliferation (Domek et al., 2016).

Hemoglobin A1c (HbA1c) is a blood test utilized to assess how well the disease is being managed. HbA1c is the glycosylated hemoglobin in the blood. It classifies the average plasma glucose concentration over a 3-month period (Zubair & Ahmad, 2018). The American Diabetes Association states that the goal for most adults with diabetes is a HbA1c less than 7% (American Diabetes Association, 2020). They also state that target levels can vary by an individual's age and other health care factors. On the other hand, the American Association of Clinical Endocrinologists suggest that treatment goal of T2DM is a HbA1c less than or equal to 6.5% (AACE, 2019). This literature review will look at the concept related to which goal is best associated with decreased infection rates, comparing HbA1C of 6.5% to 7% and higher.

The relation between glycemic control and infectious disease is not well studied (Pearson-Stuttard et al., 2016). The focus of this document will assess HbA1c and risk for

infection in diabetic patients. The case study that is outlined below focuses on a patient with poorly controlled type 2 diabetes who is found to have cellulitis due to an ulceration on her leg.

Case Report

History

A 58 year-old female presented to the primary care clinic for an episodic visit due to fever, chills, confusion and forgetfulness. The patient reported that her family had mentioned she was more forgetful than normal. Examples given by the patient included forgetting what she ate for breakfast, or where her car keys were. She reported that her fever had been present for a few days. She had taken Tylenol with some relief for a brief period of time but fever would reoccur. She cannot recount her maximum fever. She denies a cough, sore throat or ear tenderness. When asked about her history she reports being a type 2 diabetic, having coronary artery disease and a history of hypertension. She does not check her fasting blood sugars at home and denies a low carbohydrate diet or regular exercise. She denied polyuria, polydipsia, or polyphagia. Unsure if she has hypoglycemic events. Today she denies a headache or vision changes. She does not check her blood pressure at home. She denies alcohol or tobacco use, has no pertinent surgical history to report and her vaccinations are up to date. Family history includes hypercholesteremia on both sides of her family. Her home medications include Zetia 5 mg one time a day, Lopressor 50 mg daily, Lisinopril 10 mg daily, Metformin 1000 mg daily, fish oil 1000 mg daily, Zocor 80 mc daily and 325 mg aspirin daily. She states she has been taking her medications as prescribed.

Physical Examination

Her vital signs during the visit were as follows: blood pressure- 194/83, heart rate- 119, respiration rate- 14, temperature- 104.7, pulse oximetry- 93% on room air, weight- 260lb., height- 5’5”. On physical exam she was alert and answers all orientation questions correctly.

Cranial nerves intact. Her pupils were equal, round and reactive to light; Conjunctiva are normal. Her mucous membranes are pink and moist. On auscultation of her heart, she is tachycardic with regular rhythm. No murmurs heard. Lungs are clear to auscultation to bilateral lung fields with normal effort of breathing. No enlarged lymph nodes are palpated. Skin is warm and dry. Has one open ulceration to left lower extremity on the anterior portion of her shin. There was no drainage from the wound. It measures to be about 2 cm in diameter. There is redness and it feels to be hot to the touch. Pedal pulses intact. Capillary refill to reddened area is 2 seconds. Area surrounding wound had +2 pitting edema. No further wounds noted to the feet, soles of feet or other extremities.

Testing

Fasting labs were ordered including a complete blood count with differential, C-Reactive protein (CRP), lactic acid, erythrocyte sedimentation rate (ESR), HbA1c, and urinalysis. CRP and ESR were evaluated for details regarding inflammatory processes. Pertinent findings included an elevated white blood cell count (12.5 K/uL), elevated CRP (144 mg/dL), elevated fasting glucose (266 mg/dL), low sodium (132 meq/L), elevated lactic acid (4.4 mmol/L), and elevated ESR (57 mm/Hr) and a normal urinalysis. Most recent HbA1c was 9.3% three months prior to this visit.

Diagnosis, Treatment and Plan

Diagnosis for todays visit was cellulitis to the lower extremity with uncontrolled type 2 diabetes and uncontrolled hypertension. Results were discussed with the patient. She denies noting any ulceration prior to todays visit. She reports neuropathy to her lower extremities after further assessment. Treatment for this patient includes a further workup and intravenous antibiotics to be given in the Emergency Department. Common antibiotics to be used for

cellulitis include cefazolin and ceftriaxone. This patient is immune compromised and febrile with the known source of the infection being from her cellulitis. Discussed this plan with patient and she is agreeable to further management with a higher level of care. She agrees to set an appointment in clinic for one-week post hospital discharge to discuss management of her T2DM, hypertension, and infection status.

If patient refused emergency room treatment, oral antibiotics would be initiated. Cephalexin is first line for treatment of non-purulent cellulitis with dosing of 500 mg four times a day for at least five days. Would give patient teaching on when to return. This would include a new fever after current fever resolves, drawing an outline around the reddened area and told to alert the clinic if redness spreads past the line, or worsening of systemic symptoms such as increased confusion or fatigue. For further management for her T2DM, I would increase her Metformin slowly. First I would add one additional 500 mg tablet to her evening meal for a total dose of 1500mg daily. I would also schedule a recheck for another HbA1c and fasting blood glucose in 3 months after dose changes were made. Her hypertension medication Lisinopril would also need adjustment. I would increase her dose to 20 mg daily.

Literature Review

There are strong associations between T2DM and infection risks. Patients with T2DM are twice as likely to be hospitalized for infections compared to those patients without it. This is especially true for diabetics diagnosed with urinary tract infections, cellulitis, and septicemia (Li & DcDermott, 2016). Providers in clinics are typically aiming for a goal of HbA1c of 7% but that poses the question that if we lower HbA1c below 7%, does that decrease our risk for infection? The relationship between glycemic control and infectious disease is not well studied thus far (Pearson-Stuttard et al., 2016). The importance for this study remains high because it has been estimated that $612 billion are spent annually on diabetes care (Pearson-Stuttard et al.,

2016). If there is a possibility that more strict goals for T2DM treatment can help reduce infections it would be more beneficial for patients but also will save US dollars. The purpose of this literature review is to compare the concepts of infection rate and HbA1c levels to better understand evidence supporting a patient's HbA1c goal.

Evidence for Tighter Control

The *Diabetes Control and Complications Trial (DCCT)* reported infection outcomes of patients who were subjected to either a control group, where the patients received conventional therapy for DM, or in a group that received intensive therapy (Pearson-Stuttard et al., 2016). Intensive therapy was defined as target ranges for blood sugars of 80-110 mg/dL, and conventional therapy was defined at blood sugars ranging 140-180 mg/dL. These two groups were followed up every 3 months to evaluate for infection rates. The incidence of vaginal infections, foot infections, and foot ulcers were all reduced in the group that received intensive therapy (Pearson-Stuttard et al., 2016). This leads to the notion that since there was a more stringent blood sugar the patient's HbA1c was reduced in the intensive group.

Surgical Infections

In this literature review seven of the thirteen articles included evidence showing reduced infection rates with tighter glycemic control. This review observes all types of infections including post-surgical infections (Cancienne et al., 2017; Domek et al., 2016; Showen et al., 2017), wound healing after non-cardiac surgery (Chen et al., 2018), and generalized wound infections (Li & McDermott, 2016). The most common complication in elective foot and ankle surgeries was infection (42.3%) according to Domek et al. (2016). They found that the average HbA1c for patients with any type of complication after surgery within 30 days was significantly greater when compared to those without any complication. In this same study, the rate of wound

healing complications was not significant in relation to elevated HbA1C. The most significant finding from the study done by Domek et al., (2016) was that there was a "5% increase in the complication rate for every 1% increase in the HbA1C". Cancienne et al. (2017) found that the inflection point for increased risk of infection was a HbA1C of 7.5% in their study. The study included a range of HbA1C from 5.5 mg/dL up to levels of 11.5 mg/dL. Surgical site infection rates in patients with a HbA1C below 7.5% was 2.8%. Surgical site infection rates in patients with a HbA1C above 7.5% was 6.46%. Showen et al. (2017) agreed with the general consensus that there is limited data on the use of glycemic status to predict surgical site infection risk for surgeons. If surgeons used data that included measurements of HbA1c to help determine when it is favorable to operate the outcome could lead to less complications and infections in the post-operative stage. Analysis of the study done at the UCLA Medical Center in California found that there was a significantly positive association between preoperative HbA1c greater than 7% and surgical site infections (Showen et al., 2017). Chen et al. (2018) made the recommendation for future surgeries in suggesting that utilization of A1c may help predict difficult cases of uncontrolled postoperative glucose and postsurgical complications. Their study evaluated type 2 diabetics scheduled for elective surgeries. Group A had an A1c less than 7% and Group B had A1c greater than or equal to 7%. In the first week of postoperative time, nine out of fifty patients developed surgical site infections or surgical wound complications, one developed a urinary tract infection, and one had hospital-acquired pneumonia. Of the eleven total patients that developed an infection or complication, 10 patients were from group B and one was from Group A (Chen et al., 2018). This translates to elevated risk for a type 2 diabetic to develop postoperative complications if their HbA1c is greater than or equal to 7%. All of the prior stated studies can show relevance to the concept that

> Although it is widely accepted that hyperglycemia in the perioperative period is associated with surgical site infections and other complications after surgery, tight glycemic control in the postoperative period may act as a double-edged sword, increasing the risk of hypoglycemia and its associated higher mortality. (Chen et al., 2018)

In the study done by Chen at al. (2018) the median HbA1c of those who developed complications was 7.9%. The median HbA1c of those who did not develop complications was 6.5%. This leads to a conclusion that the goal for treatment would follow the AACE's guidelines.

Non-Surgical Infections

Other situations not related to surgery are also pertinent in the assessment of infection risk. The highest causes of infection are cellulitis, urinary infections, digestive infections, and septicemia (Li & McDermott, 2016). Wound infections, including cellulitis or poor wound healing remain a top concern for diabetics. One risk factor for wound complications and infection is peripheral neuropathy. Half of patients with T2DM have peripheral neuropathy (Peterson et al., 2017). When neuropathy is combined with reduced blood flow, neuropathy in the feet increases the risk of foot ulcers, infection and may even lead to limb amputation. Peterson et al. (2017) suggests that HbA1c can predict nerve degeneration and regeneration. The final result of the study conducted over a 10-year period of time was that a 1% increase in HbA1c was associated with a 1% decrease in amplitude of nerve conduction (Peterson et al., 2017). As stated prior, T2DM patients are at higher risk for wound healing complications so when the factor of neuropathy is added there is a significantly higher risk for wounds in the first place. Mor et al. (2017) had an interesting study because their analysis looked into HbA1c less than 7% at 0.5 percent increments. They also looked at HbA1c greater than 7.5% and greater at 0.5 percent increments. They found that there was an increased risk of infection for HbA1c

levels below 5.50%, and higher than 7.5%. This is data that was not found elsewhere in this literature review, because there was limited studies that analyzed below the guidelines treatment goal of 7% HbA1c. They reported that the patient group less than 5.50% was younger than the other patients and had higher numbers of comorbidities attributed to alcoholism-related conditions.

Inconclusive Evidence

Of the thirteen articles reviewed four of the articles did not show enough significant data to prove there was an association of increased risk of infection with elevated HbA1c levels. Zubair et al. (2018) had an analysis that included several factors and how they affect healing process of ulcers in diabetic patients. One of the elements they analyzed was HbA1c. They found there was an insignificant correlation of HbA1c with ulcer healing rates. Cellulitis is a soft tissue infection that often starts out from an ulceration, as seen in the case study patient in this review. In a study done by Wijayaratna et al. (2016) that focused on hospital admission for T2DM with lower extremity cellulitis, the average HbA1c for patients with cellulitis was 7.7%. Of their entire study, 22% of all lower limb cellulitis admissions were type 2 diabetics. HbA1c was not related to the risk of readmission for ulcer-related complications in type 2 diabetics. T2DM was a factor in longer length of hospitalizations but the relation between ulceration complication and glycemic control was not significant (Wijayaratna et al., 2016).

In regard to other types of infections such as those related to the eye, there was no association found with glycemic control (Ansari et al., 2017). Infections such as blepharitis, styes, periorbital cellulitis, keratitis, and lacrimal gland infection were all included on the study. The study was in agreement with common knowledge that eye infections, especially conjunctivitis, is recorded more frequently in T2DM patients, but “infection risk was in no way

found to be associated with the degree of glycemic control" (Ansari et al., 2017). Several times throughout the article by Ansari et al. (2017) the idea that there was simply not enough data to support the hypothesis that strict glycemic control affects infection rates was stated.

The review of an article related to total knee arthroplasty in diabetics did show a correlation among the level of HbA1c and surgical site infections (Hwang, 2015), but the correlation was not within strict glycemic control when using either the ADA or AACE guidelines. The conclusion from Hwang (2015) was that a HbA1c greater than or equal to 8% was associated with decreased amount of surgical site infections. Another reference used studied patients with Cystic Fibrosis-Related Diabetes (CFRD) compared to patients with Cystic Fibrosis (CF) without DM (Belle-van Meerkerk et al., 2016). In the study 39% of patients with CF were also diagnosed with CFRD and 81% of these patients with CFRD achieved target glycemic control of 7.0%. They found that infection rates were increased with certain bacteria, with lower lung functioning, and with CFRD, but did not find any correlation to well-controlled HbA1c itself (Belle-van Meerkerk et al., 2016).

A review by Pearson-Stuttard et al. (2015) included 13 studies to evaluate the association of glycemic control. One study they reviewed found that patients with a HbA1c greater than 7% was associated with higher antibiotic prescription that patients with HbA1c less than 7%. Their data analysis also reported that there was a small but non-significant difference in HbA1c at baseline in patients who were admitted to the hospital for infection. They concluded with the statement that, "evidence suggests that better glycemic control might reduce infection risk, but further longitudinal studies with more frequent measures of HbA1c are needed" (Pearson-Stuttard et al., 2015).

Discussion

This literature review has shown to have mixed conclusions. The majority of the articles used to evaluate the posed question of does a strict glycemic control affect the risk of infection provided evidence that reduces infection risk. This means that the closer a HbA1c is to either 6.5% or 7% in accordance with ADA and AACE guidelines, the lower the risk of infection. There were not enough studies to evaluate the significance of HbA1c lower than 7%. In the future, research will need to be conducted more narrowly to evaluate the infection risk when comparing the two guidelines to see which is most beneficial to the patient. If healthcare is able to give a clearer reason as to why we need patients to be in more control of their diabetes due to complication risk with surgery, or due to risk of infection they are more apt to obey the guidelines in theory.

Learning Points

- Diabetes alone is a risk factor for infection. Elevation of HbA1c greater than 7% increases risk for infection in addition to the sole diagnosis of diabetes.
- At this time there is limited data used to predict surgical site infection risk. By getting a HbA1c within 30 days of surgery, surgeons would be able to better identify those at higher risk for infection or wound complications.
- Currently there is not enough data to report what the most suitable HbA1c level is to consolidate the two guidelines of the American Association of Clinical Endocrinologists and the American Diabetes Association. Further research needs to be done to evaluate HbA1c less than 7% to determine if there is more significant association with infection rates decreasing with levels less than 7%.

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