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The effects of elevated hemoglobin A1C on cognitive function in elderly type II diabetics in the Look Ahead study

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THE EFFECTS OF ELEVATED HEMOGLOBIN A1C ON COGNITIVE FUNCTION IN ELDERLY TYPE II DIABETICS IN THE LOOK AHEAD STUDY

by

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ABSTRACT

Objective: Prolonged elevation of blood glucose levels in Type 2 Diabetes is related to a host of medical complications, most of which are mediated by micro and macro vascular damage. Importantly, diabetes is associated with accelerated cognitive decline and compromised brain health as the cerebral vasculature undergoes negative changes stemming from hyperglycemia. It is hypothesized that participants in the Look Ahead Brain study with higher HbA1c levels will exhibit worse performance on the cognitive measures, specifically on tasks assessing executive function.

Methods: Data on participants from the Look Ahead study who also participated in the Look Ahead Brain ancillary study (n = 113) were analyzed. This included HbA1c levels at year 10 (the year that participants were administered the cognitive assessment), mean HbA1c, and change in HbA1c from baseline to year. In order to assess executive function the results on two cognitive tests, the Modified Stroop Color and Word Test and the Trail Making Test, were analyzed. Then, relationships between HbA1c and performance on each of these cognitive tasks were analyzed using two approaches. First, the cohort was split into two group based on HbA1c (HbA1c ≤ 7% vs HbA1c > 7%). The latter of the two groups represented participants will poorer glycemic control. Second, linear correlations were assessed using the full range of HbA1c values as a continuous variable.
Results: There were no significant differences between HbA1c groups and performance on either of the cognitive tests. Interestingly, although not statistically significant, those with higher HbA1c levels performed slightly better on cognitive tasks. Correlation analyses revealed further trends in the direction opposite than expected, such that higher HbA1c levels were associated with better scores on both tests.

Conclusion: The surprising results of this study are evidence of the fact that a great deal has yet to be learned about the effects of T2DM and cognitive decline. There are many potential future directions for the Look Ahead Brain data, and further analyses might provide clarifications to the results of this study.
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ABBREVIATIONS

BMI .............................................................................. Body Mass Index
BP ................................................................................. Blood Pressure
CVD .............................................................................. Cardiovascular Disease
DM .............................................................................. Diabetes Mellitus
DSE ............................................................................ Diabetes Support and Education
fMRI ........................................................................ Functional Magnetic Resonance Imaging
GFR ........................................................................... Glomerular Filtration Rate
HbA1c ........................................................................ Glycated Hemoglobin
HDL-C ..................................................................... High-Density Lipoprotein Cholesterol
ILI .............................................................................. Intensive Lifestyle Intervention
LA .............................................................................. Look Ahead
LAB ............................................................................ Look Ahead Brain
LDL-C ..................................................................... Low-Density Lipoprotein Cholesterol
MI .............................................................................. Myocardial Infarction
MRI ............................................................................ Magnetic Resonance Imaging
MSCWT ................................................................. Modified Stroop Color and Word Test
RBC ........................................................................... Red Blood Cell
sMRI ................................................................. Structural Magnetic Resonance Imaging
T2DM .................................................................... Type II Diabetes Mellitus
TMT-B ..................................................................... Trail Making Test-Part B

x
TG .............................................................. Triglycerides
INTRODUCTION

*An Introduction to Diabetes Mellitus*

Diabetes mellitus (DM) affects 25.8 million people in the United States, equal to 8.3% of the American population, and Type 2 Diabetes Mellitus (T2DM) accounts for 90% to 95% of all diagnosed cases of diabetes (Prevention, 2011). Figure 1 demonstrates that the prevalence of diabetes continues to rise (Figure 1). The occurrence of T2DM continues to rise because of the aging American population, along with the fact that a majority of Americans have adopted sedentary lifestyles resulting in obesity (Sullivan et al., 2005).

![Figure 1: Number of people (in millions) diagnosed with diabetes between 1981 and 2011 in the United States. This figure demonstrates the increased incidence of DM in more recent years (Figure from Centers for Disease Control and Prevention, 2013).](image-url)
DM is a metabolic disorder characterized by elevated blood glucose levels, referred to as hyperglycemia. A healthy individual has a tightly-regulated fasting blood glucose concentration between 70-100 mg/dl, whereas a type 2 diabetic has a fasting blood glucose concentration of 126 mg/dl or higher (American Diabetes Association, 2013). The hyperglycemia that occurs in type 2 diabetics is due to four main metabolic irregularities, which include obesity, abnormal insulin secretion and function, and increased basal levels of glucose production (Weyer et al., 1999). Impairment of proper insulin function is the hallmark of T2DM (Abdul-Ghani et al., 2006).

**Pathogenesis of T2DM**

Insulin, the hormonal mediator necessary for cellular uptake of glucose, plays the important role of maintaining the body’s delicate balance between the fed and fasted states (Boron & Boulpaep, 2009). There are four main organs involved in energy metabolism: the liver, adipose tissue, skeletal muscle, and the brain (Kahn, 1994). Energy to these tissues ultimately comes in the form of glucose, the body’s principle source of fuel (Abdul-Ghani et al., 2006). In the two to four hours following a meal, also referred to as the absorptive state, the breakdown of carbohydrates into smaller sugars, such as glucose, leads to a spike in blood sugar levels (Harvey & Ferrier, 2011). Traveling in the blood, glucose makes its way to the pancreas where it prompts the glucose-sensitive beta cells to release insulin (Abdul-Ghani et al., 2006). Working as an anabolic signal, insulin targets peripheral tissues to take up glucose (Harvey & Ferrier, 2011). Insulin promotes glucose uptake in adipose tissue, the liver, and skeletal muscle
(entry into cells in the brain in not mediated) by activating insulin-sensitive glucose transporters that lie in the cellular membrane. The combination of signaling from insulin (hyperinsulinemia) plus the presence of glucose (hyperglycemia) serve to trigger glucose storage as glycogen in the tissues, as well as signal to the liver to stop glucose production (Abdul-Ghani et al., 2006). The opposite is true in the fasted state, as the drop in blood glucose and reduced insulin secretion both promote glucose production. Without the proper function of insulin these various processes are unable to adequately control blood sugar levels, as is the case in patients with T2DM.

Type 2 diabetics suffer from two significant abnormalities pertaining to insulin (Figure 2). First, the beta cells in the pancreas do not produce sufficient amounts of insulin in response to elevated blood glucose (Kahn, 1994). As was previously described, the presence of glucose in the blood stream typically causes the pancreas to secrete insulin. However, in diabetics this is not the case, as the beta cells do not adequately respond to the surge in glucose. As a result, there is not enough insulin to sufficiently trigger glucose uptake in the various tissues throughout the body. Secondly, the hepatocytes, adipocytes, and skeletal muscle cells exhibit insulin-insensitivity (Kahn, 1994). Insulin resistance refers to the inability of these target tissues to properly respond to insulin (Kahn, 1994). For unknown reasons the glucose transporters do not respond to insulin as they normally should, meaning that glucose cannot enter these cells and remains in the blood stream. Another consequence of insulin insensitivity is that the liver continues to make and release glucose. Not only are insulin levels insufficient to compensate for rises in blood glucose, but the insulin that is secreted cannot adequately
communicate with its target tissues. As a result, blood glucose levels remain elevated due to lack of proper glucose absorption and maintained glucose production. If diabetes goes untreated the hyperglycemia that persists poses a dangerous threat to every organ system.

**Figure 2: Causes of hyperglycemia in T2DM.** There are two main contributing factors to the hyperglycemia associated with T2DM. First, there is insulin-resistance in peripheral tissues, so that these cells take up less glucose. Secondly, there is insufficient production and release of insulin from the beta cells of the pancreas (Figure from Harvey & Ferrier, 2011).
**Obesity and Diabetes**

T2DM is a heterogeneous metabolic syndrome that results from a complex interplay between genetics and environment (Harvey & Ferrier, 2011). Recent trends indicate that T2DM is reaching epidemic proportions predominately due to changes in environmental factors. More specifically, the simultaneous occurrence of the obesity epidemic alongside the rise in T2DM is no coincidence (Wild et al., 2004). A body mass index (BMI) of 25 kg/m$^2$ or higher classifies a person as overweight and a BMI of 30 kg/m$^2$ is considered obese ("Overweight and obesity," 2012). More than 1/3 of US adults are obese and 1 in 6 children are obese (Figure 3).

![Figure 3: Percentage of obese adults in the US between 2011-2012.](image)

35.7% of American adults are obese (Figure from Ogden et al., 2012).
These statistics are an unfortunate consequence of increasingly sedentary lifestyles and poor nutritional choices. These behaviors have evolved over the past few decades for a number of reasons. There have been significant changes in the way that people eat, which include increased portion sizes, instead of having nightly home-cooked meals people eat out at restaurants more often, fast food chains have become more prevalent, and sugary, processed food and beverages (which are higher in calories, fat and sugar) are readily available at reduced cost ("What causes overweight," 2012). People are also less physically active. This is in part due to the conveniences of technology; for example, jobs require more time in front of a computer or on the phone ("What causes overweight," 2012). People also drive more as cities continue to increase in size, making walking or biking less feasible ("What causes overweight," 2012). In addition, the childhood obesity epidemic contributes to the growing number of overweight adults. A reduction in physical activity and poor nutrition are the driving forces behind the childhood obesity epidemic, as children who receive regular physical education at school and regularly eat well-balanced meals prepared at home have a lower incidence of obesity (Veugelers & Fitzgerald, 2005). All of these factors, along with many others, have contributed to the obesity epidemic and obesity poses a direct threat for the development of T2DM.

The most common cause of insulin resistance is obesity, but that is not to say that obesity alone causes T2DM (Kahn, 1994). While being over weight presents a direct risk for developing an insulin resistance, in order for an individual to become diabetic there must also be a defect with the beta cells of the pancreas (Harvey & Ferrier, 2011). Most
non-diabetic obese individuals exhibited increased levels of insulin, hyperinsulinemia, to compensate for the insulin insensitivity of their cells. As a result, many obese people are able to control their blood glucose levels within the same range as a healthy person (Figure 4). However, as time goes on increased demand on beta cells to produce more and more insulin can lead to their dysfunction (Weiss et al., 2005) (Figure 5). Ultimately the beta cells cannot produce enough insulin to control the blood glucose, making the individual at increased risk for T2DM. This is in part what accounts for the increased diagnosis of T2DM with old age.

**Figure 4: Insulin and glucose levels in obese versus normal weight.** As the diagram demonstrates, non-diabetic, obese individuals can initially control their blood glucose within a normal range by compensating via increased insulin production, a condition referred to as hyperinsulinemia (Figure from Harvey & Ferrier, 2011).
Figure 5: Progression from insulin resistance to T2DM. Obesity is the most significant cause of insulin resistance. However, in order for insulin insensitivity to become diabetes, the beta cells of the pancreas must become damaged, which can occur over time (Figure from Harvey & Ferrier, 2011).

Comorbidities of Type II Diabetes

The consequences of elevated blood sugar are dramatic and pervasive, resulting in both macro and micro-vascular damage. As a result, type II DM is associated with a host of other medical complications, which include, cardiovascular disease (CVD), stroke, dyslipidemia, kidney dysfunction, retinopathy and neuropathy (Harvey & Ferrier, 2011). Macrovascular changes account for increased incidence of CVD amongst diabetics. Hypertension is one of the major risk factors associated with diabetes, and is defined as a blood pressure greater than or equal to 140/80 mmHg. High blood pressure puts greater stress on the heart and causes hypertrophy of the heart muscle. Dyslipidemia is characterized as increased low-density lipoprotein cholesterol (LDL-C), decreased high-
density lipoprotein cholesterol (HDL-C), and increased triglycerides (TG), all of which can lead to atherosclerosis (American Diabetes Association, 2013). Atherosclerosis or thickening of arterial walls due to plaque accumulation has a variety of consequences. As the vessel wall stiffens and narrows the individual suffers from reduced blood flow to the heart, which puts a person at increased risk for a myocardial infarction (MI). In addition, if the plaque ruptures blood platelets are able to stick to the exposed plaque and clump together to form a clot. If a clot travels to the brain it can cause a stroke, which is the inability of oxygen-rich blood to perfuse brain tissue.

Microvasculature changes, resulting from hyperglycemia, account for damage to the retina, kidneys, and nervous system. Retinopathy refers to degradation of the microvasculature of the retina, which in severe cases can lead to blindness. Nephropathy refers to the degradation of the nephron, or functional unit of the kidney. More specifically, hyperglycemia leads to break down of the glomerulus, the structure responsible for filtration of blood into urine. As the glomeruli loose their integrity normal filtration is impeded. As a result, proteins such as albumin inappropriately end up in the urine, a condition referred to as albuminuria. Ultimately, the progression of nephropathy can hinder the efficiency of the kidneys, which is indicated by a reduction in the glomerular filtration rate (GFR). Yet another unfortunate consequence of poor glycemic control is neuropathy, which affects both the autonomic and peripheral nervous systems. Prolonged hyperglycemia can result in peripheral nerve damage, causing reduced sensation in the extremities. Neuropathy usually presents as altered sensation in the hands and feet; diabetics report an uncomfortable tingling or prickling feeling, which can
progress into reduced or lost sensation all together. As a result, diabetics are at increased risk for undetected infection or injury to their feet, which when untreated can lead to the need for amputation. It is evident that diabetes has negative consequences on every organ system. While the severity of these conditions is variable between patients, the risk for such complications rises with poor glycemic control and duration of diabetes.

*Hyperglycemia and Glycosylation*

The exact mechanism to explain how hyperglycemia causes macro and microvascular damage remains unclear. The deleterious changes to the vasculature are initially mediated by the non-enzymatic condensation of glucose to cellular proteins, which occurs in cells where the entry of glucose does not depend on insulin (Harvey & Ferrier, 2011). Glucose has the propensity to attach itself to proteins via a reaction that occurs in a two-step fashion. The first part of the reaction is reversible, whereas glucose irreversibly attaches to proteins during the second step. (Figure 6) The extent to which glycosylation occurs depends on the concentration of glucose in the blood (Harvey & Ferrier, 2011). Therefore, elevated blood sugar levels that accompany T2DM have the unfortunate consequence of producing glycated proteins. Unfortunately, the link between accumulation of glycated end products and vascular damage is not fully understood.
Figure 6: Temporary and Permanent Glycosylation of Proteins. Glucose readily attaches itself to proteins in a two-step process. The first step yields a temporary product (Schiff base), which is reversed if blood glucose levels reduce to normal. However, if hyperglycemia persists the reaction proceeds through the second step, producing the irreversible glycosylation products (Figure from Bucala & Vlassara, 1995).

An important example of this process is the formation of glycated hemoglobin (HbA1c). Importantly, red blood cells (RBC) are permeable to glucose. As a result, glucose can freely diffuse inside RBC and permanently attach itself to the hemoglobin protein. The lifespan of a RBC is about 120 days, therefore, HbA1c levels serve as an indication of blood glucose levels over a three to four month long period. A healthy individual has a HbA1c around 5%, whereas a diabetic is advised to maintain 7%. However, in populations with poorly controlled diabetes HbA1c reaches levels well above 11%. HbA1c measurements can serve as a powerful tool as it provides a look at a patient’s long-term diabetes control (Nathan et al., 1984).

Treatment for Type II Diabetes

There is a great deal of evidence that suggests that T2DM can be controlled with lifestyle changes. Diabetics are encouraged to lose weight, exercise regularly, and
maintain a healthy diet. There are also a variety of medications that are effective for the treatment of diabetes if lifestyle modification is not enough. One such drug is metformin, which functions to reduce the insulin-resistance of peripheral tissues, as well as reduce the amount of glucose that the liver produces ("Type 2 diabetes,") 2013). When metformin is not sufficient medications such as glipizide can be used to trigger insulin production and release from the pancreas. ("Type 2 diabetes,") 2013) In addition, a physician might choose to prescribe a drug like acarbose, which will interfere with the breakdown of carbohydrates in the intestine ("Type 2 diabetes,") 2013). Furthermore, if the disease worsens with time and the beta cells become compromised some diabetics require insulin injections. It is also highly recommended that patients monitor their blood sugar daily, as it is crucial that it stay within a healthy range. In addition to controlling a patient’s hyperglycemia (meaning a HbA1c less than 7%), the American Diabetes Association also recommends that diabetics keep their blood pressure (BP) below 140/80 mmHg and low-density lipoprotein (LDL) cholesterol below 100 mg/dl (American Diabetes Association, 2013).

**The Look Ahead Study**

Despite the progress that has been made in treating T2DM, the medical and financial repercussions of this illness remain numerous. As a result, countless researchers around the world have dedicated their time and resources to learning more about T2DM. One such effort is the Look AHEAD study (LA), Action for Health in Diabetes, a multicenter randomized trial designed to assess the increased risk of CVD associated with
T2DM. Based on numerous short-term studies, it is accepted that weight loss and increased physical activity are beneficial in the reduction of CVD risk factors, such as BP and cholesterol ("Clinical guidelines on," 1998). Relying on this knowledge LA set out with the primary objective to determine whether an intensive lifestyle intervention resulting in sustained weight loss would reduce CVD morbidity and mortality in older, overweight, type II diabetics. The composite cardiovascular outcome included death from cardiovascular causes, nonfatal MI, nonfatal stroke, and hospitalization for angina (Wing et al., 2013).

In 2001 LA enrolled 5000 individuals between the ages of 45-75, who had relatively well-controlled T2DM (HbA1c less than 11%) and were overweight or obese (BMI greater than 25 kg/m²) (Bertoni et al., 2008; Wing et al., 2013). Participants were randomly divided into two groups, a control and intervention. The control group, Diabetes Support and Education (DSE), attended 3 sessions per year that provided basic education on nutrition, physical fitness, and proper diabetes care. The intervention group, or Intensive Lifestyle Intervention (ILI), attended weekly treatment sessions with a multidisciplinary team and motivational meetings during the first 6 months, with reduced frequency throughout the trial (Wing et al., 2013). Counseling for the ILI group was designed to help participants adopt a rigorous weight loss regimen via reduced caloric intake (1200 to 1600 kcal per day) and increased physical activity (175 minutes of moderate exercise per week) (Wadden, 2006).

All participants had comprehensive annual health exams. Cardiovascular health was assessed with electrocardiograms, exercise stress tests (performed at years 1 and 4),
BP measurements, and blood draws (to measure HDL-C, LDL-C, and TG). Height, weight, BMI, and waist circumference were recorded. Glycemic control was assessed via measurements of blood glucose concentration and HbA1c. Renal function was evaluated with urine samples that provided levels of creatinine, albumin, and the GFR. Medication and doctor visits were recorded via interviewing. Exercise routines and eating habits were assessed with self-report questionnaires.

As was hypothesized and expected, members of the intervention group achieved significant positive changes (Figure 7). The ILI group exhibited a 1-year mean 8.5% weight loss and 21% increase in physical fitness (Pi-Sunyer et al., 2007). In addition, during the first year the ILI exhibited better glycemic control, indicated by the reduction in HbA1c (Figure 7). Furthermore, the ILI experienced improvements in all CVD risk factors including, BP, lipids, and HDL cholesterol, except for LDL cholesterol. However, these initially promising finding were not predictive of the results obtained during the 11-year follow-up period. Despite a maintained weight loss of 6% in the ILI, compared to 3.5% in the DSE, this did not translate into a sustained difference in incidence of CVD. There was no significant difference in the number of heart attacks, strokes, or deaths due to CVD between the two groups; the composite measures of CVD occurred in 403 ILI participants and 418 DSE members (Wing et al., 2013).
Figure 7: Differences in weight, physical activity, waist circumference, and HbA1c levels between DSE and ILI. Lifestyle modifications adopted in the ILI initially proved successful as the intervention group showed significant changes in comparison to the DSE. However, throughout the decade-long follow-up period differences between the two groups became less significant (Figure from Wing et al., 2013).

As a result of the findings, which negated the primary hypothesis, the LA intervention was stopped. Despite the results, this is not to say that there was no difference in cardiovascular health between the ILI and DSE groups. As Dr. Nathan, a principal investigator and director of the Diabetes Center at Massachusetts General Hospital, pointed out, “the group assigned to diet and exercise ended up with about the
same levels of cholesterol, blood pressure and blood sugar as those in the control group, but the dieters used fewer medications.” While exercise and diet alone cannot completely eliminate the risk of CVD, they can take the place of medication in certain instances (Kolata, 2012). This fact is significant as it implies that positive lifestyle choices have the ability to alter CVD risk factors enough to reduce medication use. In addition, members of the ILI sustained reduced HbA1c and as a result were less likely to be treated with insulin (Wing et al., 2013). While these are not the substantial findings that LA researchers had hoped for, it at least indicates that efforts to achieve weight loss and physical fitness are not futile. Especially in these older individuals who suffer from the numerous consequences of chronic illness, any improvement in health and quality of life is beneficial.

Despite terminating the intervention, LA has continued as an observational study, in which the ILI and DSE have been combined into a single cohort. LA provides a valuable opportunity to monitor aging in an over weight, diabetic population. The LA study refined its primary outcome to instead evaluate cognitive decline and physical function. The researchers hypothesize that there are potential long-term benefits of the 10-year lifestyle intervention, which could account for differences in cognitive function between participants originally assigned to the ILI versus the DSE.

The Look Ahead Brain Study

Prior to the changes to the LA study, the researchers were already interested in assessing cognitive function in LA participants because it is known that diabetics are at
increased risk for cognitive decline and more brain abnormalities (Biessels et al., 2008). Possible treatment strategies for preserving brain health in adults with T2DM have yet to be identified. While it has been shown that obesity is associated with reduced brain volume in healthy individuals, it is not clear whether weight loss in diabetics would convey a protective influence on cerebral health (Gunstad et al., 2008). It has been proposed that behavioral interventions that encourage regular exercise and healthy nutrition resulting in weight loss (such as the one in Look Ahead) could have positive benefits on the brain (Araki & Ito, 2009). As a result, the ancillary study Look Ahead Brain (LAB) was designed to assess the effect of weight loss on the brain health of LA participants by evaluating cognitive function and structural brain integrity. The expectation is that cognitive decline and brain atrophy will be worse in the DSE control group compared the ILI, as the intervention may have provided long-term benefits to brain health (Wing et al., unpublished).

The LAB study is being conducted at 3 of the 16 LA sites: Providence, Pittsburgh, and Philadelphia. Participation in LAB is optional, but each site has been instructed to approach all of its participants in an attempt to recruit as many people as possible. LA subjects interested in participating in LAB sign a consent form. There are three separate parts of LAB; each component of LAB is offered independently of the others so that participants can pick and choose which tests they are willing to complete.

The tasks associated with LAB include a paper-battery cognitive assessment, computer-based cognitive assessment referred to as the Toolbox, and magnetic resonance imaging (MRI) scan. It should be noted that prior to participation in the MRI portion of
LAB, participants are screened to determine whether or not they are eligible. Structural MRI (sMRI) is being used to evaluate hippocampal volume, total brain volume, and ischemic lesion volume. Hippocampal volume was selected as the primary outcome for the structural MRI for two main reasons; hippocampal atrophy is associated with obesity in type 2 diabetics, but importantly hippocampal volume is responsive to physical activity (Bruehl et al., 2009; Erickson et al., 2009). In addition, reductions in hippocampal volume are related to cognitive dysfunction (Rasgon et al., 2009). Functional MRI (fMRI) is used to assess various mechanisms through which the intervention might have affected brain function. The fMRI scans are addressing functional activation, brain networking, and cerebral blood flow. During the fMRI participants are asked to play a memory game, referred to as the N-back, which presents the subject with a continuous stream of letters, appearing one at a time, on the computer screen. Subjects play two alternating versions of the N-back game, the 1-back and the 2-back. During the 1-back participants are asked to indicate whether the letter they see on the screen is the same as the letter they saw one trial previously. During the 2-back, a slightly more challenging task, participants have to keep track of more letters and indicate whether the letter they see on the screen is the same as the letter they saw two trials previously. Measurements of functional activation, specifically in relation to working memory, provide an assessment of cognition involving the hippocampus. It has been hypothesized that the ILI, which provided subjects with better glycemic control, weight loss, and physical fitness, will be associated with greater hippocampal volume and cerebral blood flow (Wing et al., unpublished). The paper-based battery and toolbox consist of a variety of
tasks that assess vocabulary, memory, reaction time, attentiveness, executive function, visuomotor skills and cognition. Collection and analysis of LAB data is ongoing.

Effects of T2DM on Cognitive Change

Impaired glucose tolerance, hyperglycemia, insulin resistance and hyperinsulinemia all contribute to cerebral dysfunction (Araki & Ito, 2009; Messier & Teutenberg, 2005). Cognitive decline in type 2 diabetics is associated with small vessel disease in the brain (Umegaki et al., 2012). The vascular damage in the brain, which in turn leads to cognitive decline, is most likely mediated by the impairments related to insulin function and glucose tolerance. Multiple studies have demonstrated the deleterious effect of hyperglycemia on cognition. Elevated blood sugar can have toxic effects on the brain as glycation interferes with important proteins (Spauwen et al., 2013). This is supported by the findings from the Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) study, which observed that higher levels of HbA1c were associated with poorer performance on a wide range of cognitive tasks (Cukierman-yaffe et al., 2009). Umegaki et al found that while the effect of increased HbA1c measured at baseline on cognitive impairment was not significant, the level of HbA1c measured over a prolonged period of time was associated with cognitive impairment (Umegaki et al., 2012). It therefore stands to reason that diabetics with prolonged elevation of blood glucose levels are at increased risk for cognitive decline, in comparison to other diabetics with well-control blood sugar.
Interestingly, certain types of cognition seem to be affected by T2DM more than others. Executive function and information processing speed are more significantly compromised in type 2 diabetics than memory or language abilities (van den Berg et al., 2009). The results of the Maastricht Aging Study support this finding, as they observed cerebral small vessel damage caused by diabetes to be strongly associated with reduced performance in information-processing speed and executive function (Figure 8) (Spauwen et al., 2013). Furthermore, the Takahata study also observed performance on tasks that assess executive function was associated with HbA1c level (Takahashi et al., 2011). The results of the Takahata study confirmed that impaired glucose metabolism and the resulting hyperglycemia, independent of typical vascular risk factors and brain lesions that occur with aging, are associated with reduction in executive function amongst the elderly (Takahashi et al., 2011).
Figure 8: Effects of T2DM on task assessing executive function in the Maastricht Aging Study. Dark circles indicate participants without baseline diabetes. White circles indicate participants with baseline diabetes. Cognitive tests addressed information processing speed, immediate and delayed word recall (higher score indicates better performance), as well as concept shifting (lower score indicates better performance). It is evidence from the results of the Maastricht Aging Study that longer duration of diabetes is associated with reductions in information processing speed, compared to individuals without diabetes (Figure from Spauwen et al., 2013).

It is evident that the hyperglycemia associated with T2DM poses a serious threat to every organ system in the body. Perhaps most worrisome are the potential detriments to brain health. A great deal remains unclear about how T2DM is responsible for
cognitive decline, as many of the mechanisms have yet to be elucidated. There is a need for additional studies evaluating the effects of elevated blood sugar on cognitive function in type 2 diabetics, as the relationship between the two has been established but not well defined. More specifically, there is a need to more clearly identify if certain cognitive abilities are affected by diabetes more than others. This study aims to address this issue by using data on glycemic control from the LA study and assessment of cognitive function from LAB. By correlating HbA1c, a measure of hyperglycemia, with performance on certain cognitive tasks designed to assess executive function, we hope to show that elevated blood glucose has a negative impact on this specific type of cognitive performance.
Specific Aims

The objective of the current study is to look at the relationship between HbA1c levels and executive function abilities, in order to determine whether elevated blood sugar has a deleterious effect on cognitive performance. Specifically:

1. Data regarding cognitive performance will be collected on a cohort of participants in the LAB study. Candidates who have completed the paper-battery cognitive assessment will be selected for analysis.

2. Performance on two cognitive tasks that test executive function abilities, specifically, the Modified Stroop Color and Word Test (MSCWT) and the Trail Making Test-Part B (TMT-B) will be evaluated.

3. Data from the LA study regarding HbA1c will be assessed, including the level measured at the time of the cognitive exam, the mean HbA1c and change in HbA1c over the 10 year period in the LA trial.

4. Potential for statistically significant associations between HbA1c levels and participants’ scores on the MSCWT and TMT-B will be determined.

It is anticipated that this study will demonstrate a correlation between HbA1c and cognitive performance. More specifically, participants with higher mean HbA1c, which is indicative of longer-term poor glycemic control, are expected to have worse cognitive performance. It is hoped that this study provides evidence for the deleterious effects of hyperglycemia on cognition in type 2 diabetics.
METHODS

Sample

This study is an analysis of existing clinical data on 113 participants from the LA study at the Providence, Rhode Island site, who also participated in the LAB ancillary study prior to September 1, 2013. There were 68 female and 45 male participants. The mean age of participants is 69.8 years. The mean BMI at year 10 was 33.7 kg/m$^2$. All participants provided informed consent for the Look Ahead Study and the Look Ahead Brain Ancillary Study in accordance with the Miriam Hospital Internal Review Board.

Procedures

HbA1c

HbA1c levels were used to evaluate participants’ blood sugar control. HbA1c was attained from fasting blood draws taken by the study phlebotomist during annual visits. Blood draws were taken at baseline, years 1, 2, 3, 4, 6, 8 and 10.

Cognitive Task, The Stroop

In order to assess executive function, performance on the MSCWT was analyzed. The test consists of three separately administered cards (a word card, a color card, and a word-color card); the participant is asked to read each of the three cards as quickly as possible. Subtest 3 (the word-color card) of the MSCWT assesses peoples’ ability to respond to conflicting stimuli, requiring they respond to one stimulus (color) while
suppressing a reaction to the other, more prepotent, competing stimulus (word) (Stroop, 1935). The MSCWT measures processing speed and inhibition, both forms of executive function.

The MSCWT is one of the various tasks administered during the paper-battery cognitive assessment, as a part of the LAB study which participants completed during either year 10 or 11 of the LA study. The cognitive assessment was administered by one of the research assistants in a quiet room without any distractions. The examiner timed the participant while he or she completed each task.

The MSCWT consists of a series of three visual tests. During the first subtest, the participant is presented with a sheet that contains 40 word items denoting colors (red, blue, green or yellow) written in black ink. The participant is asked to read the names of the colors as quickly as possible without making mistakes. The second subtest contains 40 colored bars. The examiner asks the participant to name the colors presented on the sheet. Finally, the Stroop subtest three contains 40 word items denoting the name of a color, but each word is printed in a different color of ink. For example, the word “green” is written in blue ink. The participant is asked to name the color of the ink, not to read the word for each item. A maximum time of 120 seconds is allotted for the first two tests and 180 seconds is the limit for the third. For each subtest the time (in seconds) to recite all 40 items is recorded, along with the number of errors the participant made. A participants’ score on the MSCWT was determined based on total time in seconds to complete a subtest plus the number of errors. A higher score is considered worse, as it implies that it took a longer time to complete the test and/or more errors were made.
Cognitive Task, Trail Making

The second test of executive function that was analyzed was the TMT-B. The TMT-B was administered under the same conditions as the MSCWT. In the TMT-B participants are presented with 25 circles, which either contain a number (1-13) or a letter (A-L), dispersed non-sequentially across a sheet of paper. The respondent has to connect the circles in ascending numerical and alphabetical order, alternating between numbers and letters. The time (in seconds) to complete the task is the score. If an error is made it is immediately corrected by the examiner and accounted for in the score as it requires additional time to complete the task (REITAN, 1958). The TMT-B requires the participant to shift between the alphabetical series and numerical series, which are sets of information that are typically considered separately. The TMT-B is the most widely used assessment for executive function. It should be noted that there is also a TMT-part A, which assesses concentration and memory. TMT-A consists of 25 numbered circles dispersed on a sheet of paper; the respondent is asked to connect the circles in numerical order. While we did not analyze the TMT-A data individually, we did incorporate the score on part A in a comparison to part B for the data analysis as TMT-A may be thought of as a control for psychomotor speed and general ability to connect numbers in sequence.

Statistical Analysis

In order to investigate the relationship between HbA1c and cognitive performance on tasks assessing executive function, several statistical tests were conducted using SPSS
software. Using the ADA recommendation to define optimal glycemic control as HbA1c < 7%, the cohort was split into two groups: participants with HbA1c ≤ to 7% and those > 7% (American Diabetes Association, 2013). Participants with HbA1c > 7% were considered as having suboptimal glycemic control. As we were most interested in assessing the effect of long-term blood glucose elevation on cognitive performance, analysis was focused on mean HbA1c levels in relation to score on the cognitive tasks.

After analyzing the data in two groups, the data were then analyzed linearly. Since HbA1c levels are continuous in nature, with measurements for mean HbA1c in the current sample ranging from 5.19% to 9.01%, potential correlations between HbA1c levels were explored using the full range of these continuous data. Three different measurements of HbA1c were used. First, the HbA1c level measured at the year of the cognitive assessment was considered. The mean HbA1c across the 10-year period was used as was the change in HbA1c calculated by subtracting the value at baseline from the value at year 10.

Analysis of performance on the MSCWT was based on the score, which was generated from the difference in scores on subtest 3 and 2. In analyzing the data on TMT-B two separate measures, the score on TMT-B and the difference between the score on TMT-B and TMT-A were considered. Given that increased age is thought to be associated with poorer cognitive performance (confirmed within this sample, MSCWT Pearson R = 0.318, p = 0.001, TMT-B Pearson R = 0.427, p < 0.001) and higher BMI may be additionally related to poorer cognitive performance, both age and BMI were covaried in these analyses (Chelune et al., 1986; Elias et al., 2003; Gunstad et al., 2007).
RESULTS

HbA1c Values

The mean HbA1c of the cohort over the 10-year trial was 7.05%, ranging from 5.19% to 9.01%. The average HbA1c at year 10 (the year of the cognitive exam) was 7.18% and the range was from 5.2% to 11.5%. The mean change in HbA1c from baseline to year 10 was -0.22% and ranged from -8.4 to 4.8%. Thus on average there was a slight decrease in HbA1c levels from baseline to year 10. The cohort was split into two groups based on mean HbA1c level, n = 60 for HbA1c ≤ 7 and n = 52 with HbA1c > 7.

Cognitive Measures

The mean score on the MSCWT (score [time to complete + number of errors] on Stroop 3 minus score on Stroop 2) was 31.25, ranging from -21 to 151. The mean score on TMT-B (time to complete trails B) was 107.91 seconds and ranged from 37 to 300 seconds. The mean difference between TMT-B and TMT-A (the trails difference score) was 74.50 seconds and the range was from 11 to 269 seconds. A strong positive correlation was found between performance on the MSCWT compared to performance on TMT-B (Pearson R = 0.561, p < 0.001), as would be expected because both tests assess facets of executive function.
**HbA1c & MSCWT**

**Group differences**

The mean score on the MSCWT amongst participants in the group with HbA1c values ≤ 7% was 32.92 ± 2.72 (mean adjusted for age and BMI ± standard error) and the mean for the group with HbA1c > 7% was 29.02 ± 2.99 (Figure 8). It was observed that participants in the group with lower HbA1c had a higher average score on the Stroop, which is indicative of worse performance, however these differences were not significant [F(2,106)=0.896, p = 0.346].

**Correlations**

When the data were analyzed linearly, there were no significant correlations between either the mean HbA1c, year 10 HbA1c, or change in HbA1c and performance on the MSCWT (Table 1). We did observe a trend as mean HbA1c increased performance on the MSCWT improved (R = -0.157, p = 0.099), which was contrary to the original hypothesis.

**HbA1c & Trails**

**Group differences**

When analyzing data on the TMT-B, it was found that the mean score for participants with HbA1c ≤ 7% was 110.45 ± 8.56 and 102.02 ± 9.43 in the group with HbA1c > 7% (Figure 9). Although the directionality of this finding was also the opposite of what was expected, as participants with lower HbA1c levels performed more poorly,
the differences were not significant [F(2,106)=0.423, p = 0.517]. The means from trails difference for the group with HbA1c ≤ 7% and HbA1c > 7% were 75.65 ± 7.74 and 70.24 ± 8.52 respectively and again, these differences were not significant [F(2,106)=0.213, p = 0.646] (Figure 10).

**Correlations**

There were no significant findings other than a negative correlation between the trails difference and change in HbA1c (R = -0.193, p = .040) (Table 1). Trails difference is the score on TMT-B minus the score on TMT-A, where each score is simply the time (in second) to complete the task. Trails difference is a more accurate measurement of reaction time because it corrects for general ability to connect the dots in order. Therefore, a smaller trails difference is indicative of faster reaction time and better performance. Change in HbA1c is a measure of the difference in HbA1c level at year 10 compared to baseline. A negative change represents an improved HbA1c. Whereas a positive change in HbA1c indicates that by year 10 HbA1c was greater than it was at baseline and therefore worse. The negative relationship that we observed between trails difference and change in HbA1c means that improved HbA1c was associated with worse performance on trails.
Figures

Figure 9: Comparison of performance on MSCWT between group with a mean HbA1c ≤ 7% versus HbA1c > 7%. No significant differences in MSCWT score and HbA1c group were observed (F<1).

Figure 10: Comparison of performance on TMT-B between group with a mean HbA1c ≤ 7% versus HbA1c > 7%. No significant differences in TMT-B and HbA1c group were observed (F<1).
Figure 11: Comparison of trails difference score between group with a mean HbA1c ≤ 7% versus HbA1c > 7%. No significant differences in Trails Difference score and HbA1c group were observed (F<1).

Table 1: Correlation between HbA1c measures and performance on cognitive tests. The only significant correlation that we observed was between change in HbA1c and trails difference. *Correlations significant at the 0.05 level (2-tailed).

<table>
<thead>
<tr>
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<th>TMT-B</th>
<th>Trails Difference</th>
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<td><strong>Year 10 HbA1c</strong></td>
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<td>Significance (2-tailed)</td>
<td>p = 0.310</td>
<td>p = 0.106</td>
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</table>
DISCUSSION

Key Findings

This study contributes to the existing research on cognitive decline associations with T2DM, in an attempt to elucidate the relationship between hyperglycemia and cognitive performance. As hyperglycemia is known to have adverse health consequences, particularly on the integrity of vasculature throughout the body, we hoped to study its effect on brain health and subsequent cognitive function. More specifically, we wanted to determine if prolonged elevated HbA1c was associated with a reduction in executive function. However, when examining those who had mean HbA1c within a recommended range (≤7%) compared to those with HbA1c outside this range (>7%), there were no significant differences in performance on cognitive tasks. Although the differences were not statistically significant, the findings were surprisingly in the opposite direction from the original hypothesis. That is, a worse performance in the group with mean HbA1c ≤7% was observed. The correlation data also suggest a trend in the opposite direction than expected, but again, there was no significant relationship between the mean HbA1c level (measure over the 10-year trial in the LA study) or HbA1c measured at year 10 (the year of the cognitive exam) and performance on the TMT-B or MSCWT. These results were contrary to the original hypothesis, but can potentially be explained by limitations of the study.
**Age & BMI**

We controlled for the covariates age and BMI. Age is strongly correlated with performance on cognitive tests. As expected, a strong negative correlation was observed between age and performance on both the TMT-B and MSCWT (MSCWT Pearson R = 0.318, p = 0.001, TMT-B Pearson R = 0.427, p < 0.001). Thus as the age of participants increased, so did the time required to complete both of the tests. In addition, BMI is typically associated with reduced performance on cognitive tests. However, the opposite was found to be true; BMI was negatively correlated with time to complete TMT-B (Pearson R = -0.236, p = .013) suggesting that higher BMIs were associated with better performance (i.e., reduced time to complete TMT-B). It is possible that this unexpected relationship is due to the fact that BMI and age are negatively correlated (Pearson R = -0.339, p < 0.001). As people reach advanced ages and their health deteriorates, weight loss is a common side effect. Given these relationships, it is possible that the unexpected negative association between BMI and score could be explained because the more elderly participants who performed more poorly also had lower BMIs.

**Limitations**

It was surprising to observe a trend between higher HbA1c levels and worse cognitive performance, but this could be explained by certain limitations of the study. A potential limitation is that we did not account for medication use, specifically insulin. This might have explained why a negative correlation between age and HbA1c was observed. The fact that older participants had lower levels of HbA1c is initially
perplexing because a longer duration of diabetes is typically associated with worsening of the disease. However, this relationship could potentially be explained by the fact that older participants, who have had diabetes for a longer duration, typically end up on more medications, as well as insulin to control their HbA1c. This is supported by findings from an early analysis of LA data, which observed that older participants were more likely to meet HbA1c goals (Bertoni et al., 2008). Insulin use amongst older participants might account for lower HbA1c and in turn explain why lower HbA1c levels were associated with worse performance. We could have also controlled for duration of diabetes because duration of diabetes is often associated with reduced cognitive function (Spauwen et al., 2013).

Another potential limitation of the study is that the population in the LA study, and therefore LAB, is a group of relatively well-controlled diabetics. In recruiting participants for the study the researchers set strict selection criteria in terms of glycemic control and only accepted individuals with a HbA1c ≤ 11%. The mean HbA1c of participants in this study was 7.05%, with a range of mean HbA1c was 5.19% to 9.01%, which is indicative of a population of relatively healthy diabetics. As a result, it is possible that participants in this cohort do not have hyperglycemia that is severe enough to impact cognitive impairment detectable with the paper-based cognitive assessment. Another possible interpretation is that the damage to their cerebral health, resulting from hyperglycemia, has not yet occurred perhaps because their diabetes is relatively well-controlled. Put simply, although LAB participants have potentially higher HbA1c levels than a healthy non-diabetic population, their HbA1c levels are likely considerably lower.
than those of a broader range of diabetic individuals. It is possible that the relationship between HbA1c and cognitive function is evident only in the highest ranges of HbA1c and future studies should explore this.

Another limitation of this study and one of the significant criticisms of LAB is that there was not a cognitive assessment at baseline. Conducting the same cognitive measures pre-intervention would have allowed for proper comparisons over time. It would be useful to make within-subject comparisons to examine how cognitive performance changed over time. While it is to be expected that performance would decline with time due to the effects of natural aging, we could also account for any effect of prolonged elevation of HbA1c.

**Future Directions**

There are a variety of potential directions for the LAB data based on the implications of this study. In order to assess which regions of the brain have been affected by damage from diabetes in the LAB participants the researchers will rely on the MRI data. It would be interesting to see if participants who have compromised performance on certain cognitive tasks, particularly those testing executive function, also exhibit degeneration in brain regions thought to be involved in such processes. In addition, as other studies have shown that hyperglycemia is associated with reductions in information processing speed and executive function, we could assess whether the regions of the brain recruited during these tasks show evidence of degeneration due to T2DM in the LAB participants.
Another potential direction for LAB would be to complete another cognitive assessment in 5 years. This would allow for a comparison between the effects of T2DM, particularly HbA1c and the duration of diabetes, on cognition after 10 years in the study versus 15. Especially since so many of the participants have relatively well-controlled diabetes it would useful to see whether or not the consequences of their disease become apparent after 15 years, as opposed to 10. This could potentially provide researchers and physicians with the ability to estimate the time for the onset of cognitive decline in diabetics if they control their blood sugar within a certain (relatively healthy) range for over a decade.

It would also be useful to compare the LAB participants to an age-matched non-diabetic population. While there might not be detectable differences of the effect of hyperglycemia on cognition between LA participants (since the range of HbA1c levels was relatively small), their performance might be worse compared to non-diabetics. This would serve as evidence that elevated HbA1c has had adverse effects on the LAB population. Such findings were observed by the Takahata study, in which subjects with diabetes exhibited worse performance on tests evaluating executive function than non-diabetics (Takahashi et al., 2011).

Another potentially interesting direction for this data is the comparison of the ILI and DSE groups. It would be useful to determine whether or not there are differences pertaining to executive function between the two intervention groups. As the difference in HbA1c levels in ILI vs. DSE by the end of the 10-year trial was not substantial, if there are differences in cognition perhaps they are do to some other measure.
Conclusions

This study demonstrates the need for further research on hyperglycemia and cognitive function. The results indicate that the relationship between insulin resistance and hyperglycemia with cognitive decline is a potentially complex one. The LA study and LAB data provide a unique opportunity to study an aging diabetic population. While no one doubts the detrimental effects of T2DM, a great deal remains unknown about this increasingly prevalent chronic illness and future research is necessary to better characterize the pathogenesis of this disease.
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Research Experience

09/11 to 4/12 Nutrition and Exercise Science Lab
• Washington University School of Medicine
  Department of Physical Therapy
• St. Louis, MO
• Assisted on two community-health obesity prevention studies, worked with both child and adult subjects; responsible for teaching participants about the study, taking measurements, data entry and organization. Will be acknowledged for involvement in both manuscripts (in press.)

08/08 to 08/09 The Ben-Shahar Lab
• Washington University in St. Louis
• St. Louis, MO
• Molecular biology lab that uses Drosophila melanogaster to study the genetics of behavior. Created transgenic drosophila in order to study gene expression responsible for a peptide-gated ion channel. Performed Genomic DNA Preps, PCR, gel
electrophoresis, collected data, maintained detailed lab notes.

Medically Relevant Experiences

08/12
Shadowed a Cardiologist
- Missouri Baptist Medical Center
- St. Louis, MO
- Spent a day seeing patients with Dr. Martin Schwarze to learn more about practicing as a DO.

09/07 to 05/11
Peer Educator on Eating Disorders and Body Image
- Washington University in St. Louis, Reflections
- St. Louis, MO
- President of a campus student group that promoted served as peer educators on topics such as eating disorder, body image, and healthy lifestyle choices. Designed and organized events that addressed issues on campus such as, over exercising and cross-cultural manifestations of eating disorders.

09/10 to 12/10
Volunteer at St. Louis Children’s Hospital
- Project Picasso
- St. Louis, MO
- Volunteered on the hematology and oncology floor, made art projects with patients.

06/10
Shadowed an Endocrinologist
- Missouri Baptist Medical Center
- St. Louis, MO
- Spent a morning observing Dr. Harry Wadsworth on rounds.

05/09
Shadowed an Orthopedic Surgeon
- Missouri Baptist Medical Center
- St. Louis, MO
- Spent a day seeing patients with Dr. Jason Browdy.

09/07 to 12/09
Nutrition Committee Co-Chair
- Washington University in St. Louis, Student Health Advisory Committee (SHAC)
- St. Louis, MO
- Member of a campus student group that planned events to provide education about healthy life-style
choices on campus, specifically those dealing with proper nutrition and physical fitness.

Awards

- Dean’s List, Fall 2010
- Mortar Board Senior Honor Society, 2010-2011
- Missouri Bright Flight Scholarship, 2007-2011

Volunteer Work

02/13 to Present Rosie’s Place
- Boston, MA
- Volunteer as a tutor and substitute teacher for students studying English as a Second Language (ESL). Also work in the dining hall serving lunch and in the food pantry.

09/07 to 01/09 Dance Marathon Morale Captain
- St. Louis, MO
- Served as team leader for dancers in the annual 12-hour dance marathon fundraiser for Children’s Miracle Network.

Work Experience

07/13-Present Weight Control and Diabetes Research Center
- Brown University School of Medicine and The Miriam Hospital
- Providence, Rhode Island
- Work full time as a research assistant. Conduct annual participant visits (record answers to medical questionnaires, certified to conduct neuropathy testing and perform EKGs, take physical measurements, and administer physical function and cognitive assessments) and complete data entry for the Look Ahead study. Also responsible for assisting on studies that involved MRI. Recruit and screen participants, coordinate appointments, manage organization of data and conduct necessary behavioral testing for respective studies.

10/11 to 04/12 Varsity Tutors
- St. Louis, MO
• Worked as a private tutor for middle and high school aged students. Assisted with English, Math, History, Biology, Chemistry, and ACT preparation.