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The Role of Microvascular Complications in the Relationship between Glycemic Control and Depressive Symptomatology in Patients with Type 1 Diabetes: A Mediational Study

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The Role of Microvascular Complications in the Relationship between Glycemic Control and Depressive Symptomatology in Patients with Type 1 Diabetes: A Mediational Study

by

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Abstract

People with diabetes are at double the risk of developing depression. Depression is associated with increased morbidity and mortality in people with diabetes. Levels of A1c have been linked to microvascular complications (e.g., retinopathy, nephropathy, and neuropathy) as well as depression. The interrelationship between A1c, microvascular complications, and depression has not previously been investigated in a comprehensive model, and a better understanding of the nature of these associations is needed. Preliminary analyses test the assumption that A1c mediates the relationship between group assignment in the Diabetes Control and Complications Trial (DCCT) and microvascular complications. The primary purpose of the study is to examine multiple mediation models, which hypothesize that the severity of microvascular complications mediates the relationship between A1c and depressive symptomatology levels. Participants were people with type 1 diabetes (N = 1441) enrolled in the DCCT, a longitudinal randomized controlled trial investigating intensive insulin treatment and diabetes complications, and divided into primary (e.g., no retinopathy) and secondary (e.g., mild retinopathy) cohorts. Biological markers were used to measure A1c and microvascular complications. Depressive symptomatology was measured by the depression subscale of the Symptom Checklist-90-Revised. Simple and multiple mediation analyses were used to test proposed models. A1c mediates the relationship between DCCT group assignment and microvascular complications.

Microvascular complications partially mediate the relationship between A1c and depression for the full sample and secondary cohort. Results support the hypothesis that the severity of microvascular complications, in part, accounts for the association between A1c and depressive symptomatology in people with type 1 diabetes.

Introduction

Diabetes mellitus is an endocrinological and metabolic disease that involves the dysregulation of the use and/or the production of insulin, the hormone that is required for regulation of glucose in the body. Hyperglycemia, or elevated blood glucose levels, is the hallmark characterization of the disease (The Expert Committee on the & Classification of Diabetes Mellitus, 2003). Diabetes is a chronic disorder that affects some 24 million people in the United States, or nearly 8% of the population. It is the seventh leading causes of death in the country, and the disease doubles the risk of death for its sufferers compared to their same-aged non-diabetic counterparts (Centers for Disease Control and Prevention, 2008).

Diabetes Mellitus Classification

The overwhelming majority of diabetes cases fall into two main, etiologically distinct categories: type 1, accounting for about 5 to 10% of all diabetes cases, and type 2, accounting for about 90 to 95% of diabetes cases (Centers for Disease Control and Prevention, 2008). Type 1 diabetes, formerly known as juvenile or insulin-dependent diabetes, commonly occurs in childhood and adolescence and is considered an autoimmune disease in which beta cells of the pancreas are destroyed by the immune system. The destruction of beta cells typically leads to a complete deficiency in insulin and treatment with an exogenous supplementation of insulin is essential for survival in most cases (The Expert Committee on the & Classification of Diabetes Mellitus, 2003). Patients with type 1 diabetes must carefully monitor their blood glucose levels and inject

themselves with insulin to regulate glucose levels multiple times throughout each day to manage the disease (Executive Summary: Standards of Medical Care in Diabetes, 2009; Van Tilburg, et al., 2001).

Type 2 diabetes, formerly known as non-insulin dependent or adult-onset diabetes, is characterized by a resistance to the action of insulin, a relative deficiency of insulin production, or both. Insulin resistance leads to deficiency in the necessary insulin action required for the proper metabolism of carbohydrates, fats, and proteins (The Expert Committee on the & Classification of Diabetes Mellitus, 2003). Relative insulin deficiency means that insulin may still be produced, but the pancreas does not produce a sufficient amount of insulin needed to meet the needs of the body (Van Tilburg, et al., 2001). Autoimmune destruction of pancreatic beta cells does not occur in type 2 diabetes, as is central to type 1 diabetes, and lifestyle factors are often associated with the development of type 2 diabetes (The Expert Committee on the & Classification of Diabetes Mellitus, 2003). Although some patients with type 2 diabetes require insulin supplementation to treat their diabetes, treatment with oral medications and lifestyle modifications, including changes in diet and exercise, are often sufficient for the management of type 2 diabetes (Centers for Disease Control and Prevention, 2008; Van Tilburg, et al., 2001).

Glycemic Control

Regardless of the type of diabetes, the main goal for treatment is to reach and maintain a healthy range of blood glucose levels, often referred to as glycemic control. Hemoglobin A1c (A1c) is a weighted measure of the average blood glucose level over the past 60 to 90 days, with more weight given to the previous 30 days in the calculation

(Lustman, Griffith, Freedland, & Clouse, 1997). A1c shows the degree of glucose exposure over time and is often used to measure how well diabetes is being managed over several months (Nathan, Kuenen, Borg, Zheng, Schoenfeld, & Heine, 2008). Patients with diabetes, especially type 1, routinely test their blood glucose levels, and according to Nathan et al. (2008), there is a direct, consistent, and linear relationship between mean glucose and A1c. Therefore, A1c is a good measure of how well glucose levels are being managed over time on a day-to-day basis. Guidelines for optimum management of diabetes suggest that blood glucose levels remain as low as possible without risk of hypoglycemia or a hemoglobin A1c level of 7% or less (Qaseem, et al., 2007). Alc is such an informative value for people with diabetes that not only do practitioners set treatment goals by this number, it has recently become part of the diagnostic criteria for diabetes (Executive Summary: Standards of Medical Care in Diabetes, 2010). A1c is a better marker for the presence and severity of diabetes than single measure of glucose concentration and current standards state that diabetes should be diagnosed when an A1c value at or above 6.5% is present and a repeat of A1c testing elicits a similar value to confirm the diagnosis (The International Expert).

Diabetes Complications

Microvascular complications of diabetes, including retinopathy, neuropathy, and nephropathy, are caused by damage to and disease of the microvasculature portion, or small blood vessels, of the body. Because these diabetes-related complications can severely negatively impact quality of life and increase mortality rates, prevention, early detection, reduction, and treatment of these complications is of utmost importance for

people with diabetes and their healthcare providers. Adequate control of glycemic levels is essential for the prevention and control of these often devastating complications.

Retinopathy. Diabetic retinopathy, a term used to describe damage in the blood vessels of the eye, is the most common diabetic eye disease and one of the leading causes of blindness in adults in the United States. There are four stages of diabetic retinopathy ranging from mild, moderate, and severe nonproliferative retinopathy, to the most severe stage of proliferative retinopathy. Microaneyurisms in the blood vessels of the retina, blockage of some blood vessels that feed the retina, and advanced blockage of retinal blood vessels causing deprivation of blood to the retina are characteristic of mild, moderate, and severe nonproliferative retinopathy, respectively. Proliferative retinopathy occurs when blockage of retinal blood vessels is so severe the growth of new abnormal and fragile blood vessels is triggered which can easily break causing visual damage and even blindness (National Eye Institute, 2009). The majority of people with diabetes will experience some degree of retinopathy during the course of the disease, however there is variability in stage and severity of the retinopathy and it is in part dependent upon the duration of diabetes (Nathan, 1993).

Neuropathy. Diabetic neuropathies are nerve disorders caused by diabetes that involve damage to nerves throughout the body. Symptoms vary by type of neuropathy and by the nerve type affected and some neuropathies may be asymptomatic. Typically, symptoms start with tingling, numbness, or pain in the feet and can increase to gastrointestinal disturbance, sexual dysfunction, weakness, dizziness, and foot and hand muscle atrophy. Different categories of neuropathy exist including peripheral, autonomic, proximal, and focal. Peripheral is the most common type of neuropathy in people with

diabetes and causes pain or numbness in the extremities (i.e., toes, feet, legs, hands, and arms). Autonomic neuropathy affects nerves that control the heart, blood pressure, lungs and eyes and can cause bladder, gastrointestinal, and sexual dysfunction and may preclude the signs of hypoglycemia from occurring. Proximal neuropathy may lead to pain and weakness in the leg and buttocks area, and focal neuropathy is characterized by sudden pain or weakness of the muscle and can affect any nerve throughout the body (National Diabetes Information Clearinghouse, 2009).

Nephropathy. Diabetic nephropathy is damage to or disease of the kidneys that is thought to develop as a complication from a combination of elevated blood sugar levels and hypertension. Excessive blood sugar may damage and destroy nephrons, the units of the kidney that filter waste from the body. Eventually, as more nephrons are destroyed albumin protein may leak from the kidney and into the urine. Nephropathy is a progressive disease that is the leading cause of long-term kidney failure and end-stage kidney disease in the United States and a major cause of illness and even death in people with diabetes. Patients with nephropathy often require dialysis or kidney transplantation (American Diabetes Association 2004).

Glycemic Control and Diabetes Complications

A1c is considered a value of central concern in the diagnosis and evaluation of management in diabetes largely because of a strongly established link between glycemic control and long-term diabetes complications. This connection is the basis for the recommendation of maintaining an A1c value below 7.0% and regular monitoring of A1c levels. A myriad of previous studies have linked poorly controlled A1c levels to

numerous microvascular diabetes complications including diabetic peripheral neuropathy, retinopathy, and nephropathy, among other types of complications.

The Diabetes Control and Complications Trial (DCCT). The Diabetes Control and Complications Trial (DCCT) was a multicenter randomized longitudinal controlled clinical trial designed to investigate the influence of intensive exogenous insulin treatment for people with type 1 diabetes on the development and progression of long-term diabetes complications. The study was designed to examine the effects of standard versus intensive insulin treatment on the development, progression, and/or resolution of early vascular complications in patients with type 1 diabetes. Two groups of participants were enrolled and randomized to either the intensive or standard treatment groups. The primary intervention group included participants with no background retinopathy and the secondary intervention group included participants with minimal or low levels of background retinopathy. Development of microvascular complications was investigated in the primary prevention group, whereas the progression and resolution of vascular complications was investigated in the secondary prevention group. The goal for the experimental group was to maintain blood glucose levels as close to the normal nondiabetic range as safely possible, with a target A1c level of less than 6.5%. This was achieved with a minimum of three daily insulin injections or use of an insulin pump for participants in the intensive treatment group. In contrast, standard care group participants had only one to two insulin injections daily (DCCT Research Group, 1993a; DCCT Research Group, 1993b). A more detailed description of the study is presented below in the procedures section.

The DCCT was carried out over more than a 10-year period, with continuous enrollment over a 6 year period, and provided definitive evidence demonstrating the role of glucose control in the onset, development, and progression of diabetes related complications. Intensive insulin treatment lead to significant reductions in glycemic levels for patients with type 1 diabetes and the lowest A1c level for the intensive treatment group was reached at 6 months into the study (DCCT Research Group, 1993a). A1c levels were significantly lower in the intensive treatment group relative to conventional treatment groups after baseline and until the end of the study. Intensive insulin treatment lead to significant reductions in glycemic levels for patients with type 1 diabetes and the lowest A1c level for the intensive treatment group was reached at 6 months into the study (DCCT Research Group, 1993a).

Effect of DCCT A1c reduction on retinopathy. Results of the DCCT showed that intensive insulin therapy initially led to transient worsening of retinopathy, especially in the secondary-intervention cohort during the initiation of therapy. However, these abnormalities tended to disappear after about 18 months of treatment. Risk of progression of retinopathy was reduced for patients with early worsening who received intensive therapy as compared to those in the standard treatment group (DCCT Research Group, 1993a; DCCT Research Group, 1995c; DCCT Research Group, 1995d). Cumulative retinopathy incidence was not significantly different between the two treatment groups until about 3 years of treatment for both the primary and secondary-prevention cohorts. At the 5 year point and onward the cumulative incidence of retinopathy was about 50% lower for the intensive therapy group than the conventional therapy group in the primary-prevention cohort. Intensive therapy reduced the average adjusted risk of retinopathy by

76% and risk reduction increased over time in the primary-prevention cohort. In the secondary-prevention cohort, intensive therapy reduced the average risk of retinopathy progression by 54% over the duration of the study (DCCT Research Group, 1993a; DCCT Research Group, 1995c; DCCT Research Group, 1995d).

Effect of DCCT A1c reduction on nephropathy. Diabetic nephropathy is initially manifested as microalbuminuria, or an increase in urinary albumin excretion. It then progresses to overt albuminuria followed by renal failure (Krolewski, Laffel, Krolewski, Quinn, & Warram, 1995). In patients with type 1 diabetes, the risk of microalbuminuria is strongly related to the degree of hyperglycemia and the risk grows significantly higher with A1c levels above 10% (Krolewski et al., 1995). Intensive therapy in the DCCT resulted in lower rates of microalbuminiuria and albuminuria in both cohorts as compared to the conventional therapy group. The risk of microalbuminuria was reduced by 34% and 43% for the primary-prevention and secondary-intervention cohorts in the intensive treatment group, respectively. For the combined cohort, the risk of albuminuria and microalbuminuria was reduced by 54% and 39% percent, respectively, with the use of intensive insulin therapy (DCCT Research Group, 1993a; DCCT Research Group, 1995b).

Effect of DCCT A1c reduction on neuropathy. The appearance of clinical neuropathy, defined by either abnormal autonomic-nerve testing or abnormal nerve conduction in two or more peripheral nerves plus abnormal neurologic examination, was reduced by intensive insulin therapy by 69% and 57% for the primary-prevention and secondary-intervention cohorts without baseline neuropathy, respectively, as compared to their conventional treatment counterparts. Similar reductions in the individual

components used to evaluate the presence of clinical neuropathy were also seen with intensive therapy (DCCT Research Group, 1993a; DCCT Research Group, 1995a). Even after discontinuation of the DCCT, an eight-year follow up of DCCT participants in the observational Epidemiology of Diabetes Interventions and Complications (EDIC) showed a continued higher rate of incidence of signs, symptoms, and clinically diagnosed neuropathy in participants formerly in the conventional treatment group compared to those receiving intensive treatment. The higher incidence rates occurred despite the narrowing and eventual disappearance of glycemic differences between the two groups (Martin et al., 2006).

UK Prospective Diabetes Study (UKPDS). Similar findings were reported by the UK prospective diabetes study (UKPDS). The UKPDS was a clinical trial that examined the effect of intensive blood glucose control in over 4000 people with type 2 diabetes. The relationship between glycemic exposure and diabetes related complications were similar to those in the DCCT and EDIC. In the prospective study of people with type 2 diabetes, each 1% reduction in A1c was associated with a 21% reduction in risk of any diabetes related end point, including microvascular complications, macrovascular complications, and death. Specifically, a 37% decrease in risk for microvascular complications occurred with each 1% decrease in A1c level, providing further support of the relationship between glycemic exposure and diabetes related complications (Stratton et al., 2000). In summary, research consistently shows a strong predictive association of elevated glycemic control levels and greater incidence and severity of diabetes related complications (Diabetes Control and Complications Trial Research Group, 1993; Gaster

& Hirsch, 1998; Klein, Klein, & Moss, 1996; Klein, Klein, Moss, Davis, & DeMets, 1988; Stratton, et al., 2000)

Depression

Depression can refer to a transient mood state, a constellation of symptoms, and two clinical diagnoses with strict diagnostic criteria (major and minor depression). Studies in this area typically examine the extent of depressive symptoms or the presence or absence of a clinical diagnosis (major depression or minor depression). Major and minor depression are classified psychological mood disorders, with major depressive disorder affecting approximately 7% of the general population in a given year (Kessler, Chiu, Demler, & Walters, 2005). The central characterization of depression is either a depressed mood or loss of interest or pleasure over a 2-week period. Other symptoms include fluctuations in weight and/or appetite, fluctuations in sleep patterns, psychomotor agitation or retardation, fatigue, feelings of worthlessness or excessive guilt, concentration difficulties, and suicidal ideation, plans, or attempts.

Depression and Diabetes

Depression rates have been estimated to be upwards of twice as high in the diabetic population than in the general population. In their 2001 meta-analytic study of the prevalence of comorbid depression in adults with diabetes Anderson and colleagues analyzed over 40 studies and found the odds of depression in participants with diabetes were twice that of their non-diabetic control counterparts (Anderson, Freedland, Clouse, & Lustman, 2001). This doubled odds ratio of the prevalence of depression in the diabetic population compared to the non-diabetic population was independent of sex, diabetes type, subject source, or assessment method.

The co-occurrence of depression and diabetes is significant because previous research suggests that the comorbidity is associated with a host of problems including poorer medical regimen adherence, increased functional impairment (Ciechanowski, Katon, & Russo, 2000), greater symptom burden (Ludman, et al.), higher health care costs (Egede, Zheng, & Simpson, 2002), and increased mortality rates (W. Katon, et al., 2008; W. J. Katon, et al., 2005). One study by Katon and colleagues (2008) found a 36% to 38% increased risk for all-cause mortality for diabetic patients with comorbid depression compared to their non-depressed diabetic counterparts. A separate study by Katon and colleagues (2005) suggests that both major and minor depression increase mortality rates for diabetics with comorbid depression compared to nondepressed diabetics by nearly two-fold.

Glycemic Control and Depression

As noted earlier, Hemoglobin A1c (A1c), a weighted measure of the average blood glucose level over the past 60 to 90 days is typically used to measure how well diabetes is being managed over several months (Lustman, Griffith, Freedland, & Clouse, 1997; Nathan et al., 2008). The American Diabetes Association recommends a treatment goal of A1c <7% (2009), which would be indicative of good glycemic control. Higher values of A1c would be indicative of poor glycemic control (American Diabetes Association 2009).

A1c levels have been linked to depression levels in numerous studies. In their 2000 meta-analytic review of the relationship between depression and glycemic control, Lustman and colleagues (Lustman, Anderson, Freedland, de Groot, Carney, & Clouse, 2000) analyzed 24 cross-sectional studies with a total of 2,817 participants with both type

1 and type 2 diabetes. The authors found a significant positive relationship between depression and A1c, with a small-to-moderate overall effect size. While this study provides further confirmation for the existence of a relationship between depression and hyperglycemia, the cross-sectional nature of the data precludes the ability to determine either directionality of this relationship, or mechanisms explaining the relationship between the two.

Opposing theories have been proposed regarding the nature of the relationship between depression, glycemic control, and related physical complications. These competing theories suggest that depression can be either an antecedent to or a consequence of symptoms and medical complications related to glycemic control. The antecedent model suggests that depression adversely influences behavioral (e.g., diabetes self-care) and physiological mechanisms (e.g., activation of the HPA axis) that result in poorer glycemic control and, subsequently, a greater incidence and severity of diabetes complications. (William P. Sacco & Bykowski, 2010). An alternative theory suggests that depression is a consequence of poor adherence and/or diabetes medical symptoms resulting from poor glycemic control. The consequence model suggest that failure to effectively adhere to the complicated diabetes self-management regimen leads to negative self-relevant cognitions (e.g., low self-efficacy), poorer glycemic control, and increased incidence and severity of medical complications. Depression results from these experiences. For example, Sacco, Wells, Friedman, Matthew, Perez, and Vaughan (2007) found that body mass index (BMI; an indicant of adherence in people with type 2 diabetes) was associated with diabetes medical symptoms and depression in people with

type 2 diabetes. Diabetes symptoms mediated the relationship between BMI and depression, providing support for the consequence model.

Similarly, Sacco and Bykowski (2010) found that A1c was associated with depression levels in people with type 1 diabetes, and participants' thoughts about their ability to effectively manage their disease (diabetes self-efficacy) mediated this relationship. This finding is consistent with the proposal that depression occurring in people with type 1 diabetes may be a consequence of negative cognitive appraisals resulting from their ability to keep their A1c levels at healthy levels.

Diabetes Complications and Depressive Symptomatology

Diabetes complications have been linked to increased levels of depression and depressive symptomatolgy within the diabetic population. In their 2001 meta-analytic study of the association of depression and diabetes complications de Groot and colleagues attempted to evaluate the strength and consistency of this relationship (de Groot, Anderson, Freedland, Clouse, & Lustman, 2001). Additionally, they sought to determine if the relationship between diabetes complications and depressive symptoms differed by diabetes type. The authors examined a total of 27 studies that evaluated the relationship between depression and at least one complication of diabetes including diabetic retinopathy, diabetic neuropathy, diabetic nephropathy or end stage renal disease, macrovascular complications, and sexual dysfunction.

Overall, the authors found a moderate effect size for the relationship between depression and all diabetes complications. Moderate effect sizes were found for the relationship between depression and all individual diabetes complications (i.e., nephropathy, neuropathy, sexual dysfunction, and macrovascular disease alone) apart

from retinopathy for which a small to moderate effect size was found. Overall, higher depression levels were associated with higher numbers and greater severity of diabetes related complications. Additional analyses indicated that greater numbers of complications were associated with higher depression levels. Further, moderator analyses by diabetes type (i.e., type 1 and type 2) indicated similar moderate effect sizes for both types. The similar effect size for the relationship between depression and diabetes complications in patients with type 1 and type 2 diabetes suggests that common pathways may exist to explain this association despite the disparate physiological manifestations and distinctions of these diseases. Despite the consistent relationship found between depression levels and the presence and severity of diabetes complications, all of the studies included in the meta analysis are cross sectional (de Groot et al., 2001). Therefore, the temporal relationship between depression and diabetes complications is not elucidated through these findings .

Current Study

Meta-analytic methods have provided evidence that people with diabetes are at a two-fold increased risk of depression relative to their non-diabetic counterparts (Anderson et al., 2001). Myriad studies, including large-sample, longitudinal, and experimental studies (DCCT Research Group, 1993a) have demonstrated a consistent relationship between glycemic control and diabetes-related microvascular complications. Poor glycemic control, as measured by elevated A1c levels, is consistently linked to greater occurrence and severity of diabetic complications including retinopathy, neuropathy, and nephropathy. Meta-analyses also show a consistent relationship between glycemic control and depression (Lustman et al., 2000), with poorer glycemic control

associated with increased levels of depression and depressive symptomatology. Meta-analytic techniques also demonstrate a consistent relationship between diabetes related complications and depression, with a positive relationship between the number and severity of diabetes related complications and levels of depression and depressive symptomatology (de Groot et al., 2001).

Previous research has demonstrated a positive relationship between A1c and diabetes complications, A1c and depression, and diabetes complications and depression. However, the mechanisms explaining the glycemic control and depression connection have not yet been elucidated. Additionally, although the available literature shows consistency with the relationships between glycemic control, diabetes complications, and depression levels, several limitations exist. Most studies address the relationship between two of these variables but do not provide a model examining the relationship between all three, leaving the interrelationship between A1c, microvascular diabetes complications, and depressive symptomatology unclear. Furthermore, competing theories exist regarding the nature of the relationship between diabetes related health complications and depression. The antecedent model suggests that depression may contribute to physiological and behavioral changes that negatively influence glycemic control and, therefore, symptoms and complications. The consequence model suggests that depression occurs consequentially to increased medical symptoms and complications that arise from poor glycemic control (Sacco et al., 2007; Sacco & Bykowski, 2010). Further studies within these theoretical frameworks are needed to elucidate the nature of the relationship between these variables. Furthermore, current literature is largely based on cross-sectional data precluding the ability to elucidate the temporal relationship between these

variables. With the exception of longitudinal experimental studies showing that better glycemic control can delay the onset and reduce the severity of diabetes complications (DCCT Research Group, 1993a), the cross-sectional nature of much of the research in this area does not allow for conclusions about the temporal nature of the relationships to be drawn.

The current study seeks to address the limitations of previous research by analyzing the relationship between A1c, microvascular diabetes complications, and depressive symptomatology in meditational models using longitudinal experimental data based on an a priori theoretical framework. The role of diabetes related complications as a mechanism explaining the relationship between A1c and depressive symptomatology were explored in the current study within the depression-as-consequence model.

First, preliminary analyses of the effect of DCCT group assignment (intensive treatment versus control) on the presence and severity of microvascular complications were evaluated in three separate models (analyzing each microvascular complication independently), evaluating A1c as a mediator of the treatment effect. These analyses were intended to test the assumption that A1c is the mechanistic variable explaining the relationship between DCCT group assignment and lower incidence and severity of diabetes related complications and provide evidence for the nature of the relationship between DCCT treatment group, A1c, and microvascular complications. These models will also help to establish a foundation for further analysis of the relationship between A1c, microvascular complications, and depression. The depression-as-consequence model was then evaluated in a separate multiple-mediator model with A1c predicting

later depressive symptomatology, and microvascular complications examined as mediators of the relationship between A1c and depression.

Four main hypotheses were proposed to test preliminary analyses of the relationship between DCCT treatment condition, A1c, and diabetes related microvascular complications, as depicted graphically in Figure 1. First, treatment group was expected to affect the incidence and severity of diabetes complications, with decreased incidence and severity of each complication found in the intensive treatment group. Second, intensive treatment condition was expected to result in lower A1c values. Third, A1c was expected to be positively related to the incidence and severity of the microvascular diabetes related complications of retinopathy, nephropathy, and neuropathy. Fourth, it was predicted that the effect of treatment condition on the incidence and severity of microvascular complications will be fully mediated by A1c. These hypotheses were tested through three simple-mediation models for each microvascular diabetes related complication.

Four main hypotheses were proposed for the relationship between A1c, microvascular diabetes related complications, and depressive symptomatology, as depicted graphically in Figure 2. First, it was expected that A1c will be positively associated with levels of depressive symptomatology. Secondly, A1c was expected to be positively related to the presence and severity of diabetes related microvascular complications of retinopathy, neuropathy, and nephropathy. Third, microvascular diabetes complications were expected to be positively related to depressive symptomatology. Lastly, it was predicted that the presence and severity of microvascular diabetes related complications will fully mediate the relationship between A1c and

depressive symptomatology. These hypotheses were tested in a single multiple-mediator analysis.

Method

This study utilized data from the Diabetes Complications and Control Trial (DCCT). The DCCT was a 29 center, randomized clinical trial that compared the effects of intensive diabetes therapy to standard treatment on the development and progression of complications among individuals with type 1 diabetes. The study was designed to examine the effects of standard versus intensive treatment on the development, progression, and/or resolution of early vascular complications in patients with type 1 diabetes. Participants were categorized as either primary or secondary prevention group participants based on the absence or presence of minimal diabetic retinopathy, respectively, at study initiation (DCCT Research Group, 1986). The study, funded by the National Institute of Diabetes and Digestive and Kidney Diseases, was initiated in 1983 and ended in 1993.

Participants

Participants included 1441 generally healthy people with type 1 diabetes who ranged from 13 to 39 years of age at the time of randomization. Of the 1441 participants, 726 who had no diabetic retinopathy were considered primary prevention participants, and 715 who had minimal background diabetic retinopathy at the start of the study were considered secondary prevention subjects. For the primary prevention group participants, eligibility requirements included type 1 diabetes duration for at least one year but no more than five years, absence of diabetic retinopathy, visual acuity of at least 50 letters in both eyes, and less than 40 mg albumin per 24 hours on a four-hour standardized urine

collection. Eligibility criteria for secondary prevention subjects included type 1 diabetes duration of at least one year but no more than 15 years, presence of at least one microaneurysm in either eye but less retinopathy than would characterize either eye as P2 or worse based on central grading of stereo fundus photographs, visual acuity of at least 45 letters in both eyes, and 200 mg or less albumin per 24 hour on a four-hour standardized urine collection (DCCT Research Group, 1993b). See Table 1 for full demographic information and baseline descriptive values for the full sample, and primary prevention and secondary intervention cohorts.

Exclusion criteria for the study participants were: previous intensive insulin treatment; C-peptide levels greater than .2 or .5 pmol/ml for participants with type 1 diabetes duration greater than 5 years or less than 5 years, respectively; insulin resistance; three or more episodes of diabetic ketoacidosis requiring hospitalization in the year before randomization; pregnancy or plans for pregnancy within 2 years of randomization; hypertension; hyperlipidemia; urinary tract infection;, history of drug or alcohol abuse during the five years prior to randomization; diabetic neuropathy, hypothyroidism; obesity as defined as a body weight greater than 130% of ideal body weight; chronic disease requiring medication for greater than 4 months during the year before randomization; history of coronary heart disease or symptomatic peripheral vascular disease; history of epilepsy or seizures requiring medication; presence of serious mental disorders that would interfere with protocol adherence; among other criteria (DCCT Research Group, 1993b).

Materials

Depressive symptomatology. The *Symptom Checklist 90-Revised* (*SCL-90-R;* Derogatis, 1994) was used to measure depressive symptomatology. The SCL-90-R is a 90-item self-report symptom inventory and is a widely used measure of current psychiatric symptoms. It is designed to screen a broad range of psychological problems in nine primary symptom dimensions, including: Somatization, Obsessive-Compulsive, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid ideation, and Psychoticism. Additionally, overall psychological distress is measured by the Global Severity Index, the Positive Symptom Total, and the Positive Symptom Distress Index. Each item is rated on a five-point Likert-type scale of overall distress level with scores ranging from 0 ("*not at all*") to 4 ("*extremely*").

The 13 item depression subscale of the SCL-90-R was used to assess the extent to which participants experienced depressive symptoms during the past 7 days. A range of depressive symptoms were assessed, including dysphoric mood, anhedonia, loss of energy, feelings of hopelessness, and thoughts of suicide. Participants rated the severity of their depressive symptomatology experiences over the past week on a 5-point scale ranging from 0 ("*not at all*") to 4 ("*extremely*"). Total subscale scores are calculated by a summation of the item responses, and raw scores can be derived by dividing the total score by the number of items on the scale (i.e., 13 for the depression subscale). High internal consistency ($\alpha = .90$) has been reported for the depression subscale of the SCL-90-R (Derogatis, 1994; Derogatis & Savitz, 1999) .Adequate to good test-retest reliability has been established with 1-week ($r = .82$) and 10-week ($r = .75$) intervals between testing (Derogatis; Derogatis & Savitz). The validity of the depression subscale of the

SCL-90-R has been demonstrated through high correlations with other measures of depressive symptomatology, including the Beck Depression Inventory (Peveler & Fairburn, 1990). The full SCL-90-R depression subscale can be seen in Appendix A.

Neuropathy. Clinical and electrodiagnostic criteria were used to determine the presence of neuropathy. Neurological evaluations were performed by neurologists blinded to treatment group assignment. Any non-diabetic causes of neuropathy were identified. Table 2 provides detailed diagnostic criteria and diagnostic categories (DCCT Research Group, 1995a). Further details are provided in Appendix B.

A 3-point rating scale was used to determine participant neuropathy level. Participants were classified as either having definite neuropathy (1), possible neuropathy (2), or no neuropathy (3). Definite neuropathy was confirmed by the presence of at least two of the following: physical symptoms, abnormalities on the sensory examination, and/or absence or decrease in deep-tendon reflexes. Participants with only one abnormal finding among physical and sensory symptoms and deep-tendon reflexes, with or without abnormal nerve conduction, were classified as having possible clinical neuropathy. All other participants were classified as having no neuropathy present (Albers, et al., 2007).

Retinopathy. Retinopathy was measured by an assessment of the grading of severity of lesions of diabetic retinopathy for each eye every six months. Lesion grades were used to determine overall severity of retinopathy according to Early Treatment Diabetic Retinopathy Study (ETDRS) interim and final scales. Seven-field stereoscopic color fundus photographs were independently graded by two graders masked to treatment for rating reliability. Grades that differed by two or more steps were assessed by a senior grader who assigned a final grade and a single grading was completed for photographs

from nonannual follow-up visits. Additionally, sets of photographs were periodically regraded to ensure reproducibility of the grading system. Agreement comparisons were complete in 53.3% to 67.6% of cases, within one step 84.3% to 95.0% of cases, and within two steps 96.2% to 98.3% of comparison cases (DCCT Research Group, 1995b). Retinopathy severity ratings ranged from a scaled score of 10 to a scaled score of 85, indicative of the absence of diabetic retinopathy to advanced proliferative diabetic retinopathy or partially obscured fundus, respectively. A 10-point scale ranging from 1 to 10 was used to indicate retinopathy severity based on scaled score ratings. Severity ratings included no retinopathy, very mild, mild, moderate, and severe nonproliferative diabetic retinopathy, and mild, moderate, high-risk, and advanced proliferative diabetic retinopathy (DCCT Research Group, 1995d). Definitions of the ETDRS severity levels of retinopathy for can be seen in Table 3. The ratings of retinopathy levels for each individual eye as based on the ETDRS severity level (Table 3) were used to determine overall retinopathy severity level for the person (Table 4). Change over time in retinopathy severity was a primary outcome of the DCCT. Sustained progression of retinopathy was considered present with a cumulative increase by three or more steps on the scale at two consecutive visits, shown in Table 4.

Nephropathy. Nephropathy level was measured at annual follow-up visits through urine collection over a four-hour collection time period. Urine samples were obtained after participants had breakfast and their morning insulin dose and while they were resting and in a sitting position. Participants were asked to avoid caffeinated beverages the day of and strenuous exercise during the day prior to testing. The level of nephropathy was determined by measurement of Albumin Excretion Rate (AER) in units

of mg/24 hours and standard Creatinine Clearance in units of ml/min. Participants were categorized into a six-point nephropathy level scale based upon AER and Creatinine Clearance levels. An AER less than 40mg/24 hours is indicative of level 1 nephropathy, and an AER greater than 300 mg/24 hours and a Creatinine Clearance level below 70 ml/min was indicative of level 6 nephropathy (See Table 5; DCCT Research Group, 1995b).

A1c. Glycosylated hemoglobin (A1c) was measured at baseline, at quarterly visits, and at study closeout for participants in the standard treatment condition. Participants in the intensive treatment group had A1c measured at baseline, monthly visits, and study closeout. Blood samples for A1c were assayed in the Central Biochemistry Laboratory.

Procedure

Participants were randomized to either standard or intensive diabetes therapy and followed for an average of 6.5 years (DCCT Research Group, 1993a; DCCT Research Group, 1993b). Patients assigned to the standard diabetes management group had one to two daily insulin injections with daily self-monitoring. Additionally, patients in the standard therapy group received an individualized meal plan with dietitian reinforcement every six months, an education program, and standard clinic visits and monitoring at three month intervals (DCCT Research Group, 1993b). Patients in the intensive treatment group received a minimum of three daily insulin injections or used an insulin pump with self-monitoring of blood glucose a minimum of four times daily. They received the same dietary management principles as the standard therapy group with reinforcement from the dietitian as often as necessary to attain treatment goals. Additionally, patients in the

intensive treatment group had weekly clinic visits until stabilization of their diabetes treatment program followed by at least monthly clinic visits for medical and psychological supervision. Intensive treatment also involved daily telephone contact for self-management review and adjustment during the first week of the trial followed by monthly telephone calls. Staff was also available at each clinic for patients in the intensive treatment group to contact via telephone 24 hours a day. The aim of the intensive treatment group was to achieve and maintain normal or as close to normal glycemic control, or below 6.5% (DCCT Research Group, 1986).

Participants attended study clinics quarterly. A1c was measured at quarterly visits, retinopathy severity was measured at 6 month intervals, and both nephropathy and depressive symptomatology were measured annually. Neuropathy was measured through a standardized neurologic history and physical examination by neurologists at baseline, 5 years, and at the close out of the study.

Statistical Analysis

Four models were be tested for this study for the full sample and the primary, as well as for secondary intervention cohorts separately. First, three simple-mediation models were tested evaluating the meditational role of A1c in the relationship between DCCT treatment group assignment (intensive or standard treatment) and the presence and severity of microvascular diabetes related complications (see Figure 1). Each diabetes complication (i.e., retinopathy, nephropathy, and neuropathy) was tested independently as an outcome in the simple-mediation model. The models were tested longitudinally, with A1c measurement points preceding each diabetes complication measurement point. Level of glycemic control, as measured by A1c, was be averaged over the 4^{th} and 12^{th}

quarterly visit (between years 1 and 3 of study participation) of the DCCT to capture the early change in glycemic control expected to be achieved by intensive insulin treatment. Average levels of microvascular diabetes complications between the 16th and 21st quarterly visit (between years 4 and 5.25 of study participation) were analyzed in each model. This time range captures the greatest variability in the data because diabetes complications tend to occur increasingly with disease duration. DCCT inclusion requirements precluded people with advanced retinopathy from participating in the study. Therefore, many complications will not occur until later years in the study. Additionally, neurologic history and physical examination for neuropathy was measured at baseline, 5 years, and study end only, so it is important to have a range that captures this data.

A multiple-mediator model was used to examine the relationship between A1c, microvascular diabetes complications, and depressive symptomatology (see Figure 2) to provide further evidence of the nature of this relationship over time within the depression-as-consequence-model framework. Within the longitudinal model, measures of A1c preceded measures of diabetes complications, and measures of complications preceded depressive symptomatology measures. Measurement points for A1c and microvascular complications for the multiple-mediator model were averaged over the same time points as the simple mediator models previously stated. Depressive symptomatology, as indicated by total scores on the depression subscale of the *SCL-90-R*, was averaged between the 23rd and 28th quarterly visit (about 6 years into the study) to capture the most data for participants who's depressive symptom levels were not measured exactly on the 24th quarterly visit.

The models were tested using the mediation bootstrapping Sobel extension method as described by Preacher and Hayes (2004 & 2008). Bootstrapping is a nonparametric statistical approach that is the most powerful method of obtaining confidence limits for specific indirect effects of mediation without assumptions of sampling distribution. The multiple resampling bootstrapping methods of the analyses of mediator models do not assume normality of the sampling distribution of the indirect effect of the independent variable (IV) on the dependent variable (DV) that other methods, such as the product-of-coefficients strategy, assume (Preacher & Hayes, 2004, 2008).

Simple mediation models were used to test the relationship between group assignment (IV), A1c (mediator) and diabetes complications (DV; Preacher & Hayes, 2004). A multiple-mediator model was used to test the meditational impact of the microvascular diabetic complications, retinopathy, neuropathy, and nephropathy (mediators) on the relationship between A1c (IV) and depressive symptomatology (DV). Testing multiple mediator models provides specific indirect effects of the ability of a given mediator to uniquely mediate the effect of the IV on a DV controlling for all other mediators in addition to total indirect effects. Relevant variables including gender, age, baseline depressive symptomatology, baseline A1c level, baseline diabetes complications severity (i.e., level of retinopathy, baseline albumin excretion, and neuropathy ratings), duration of diabetes, and smoking status were controlled for in each of the four mediation models tested. Baseline retinopathy levels were not controlled for the primary intervention cohort because inclusion requirements precluded the presence of retinopathy in this group.

The simple mediation models answers the four hypotheses regarding the relationship between DCCT group assignment, A1c, and diabetes related complications for each diabetes related microvascular complication by providing the direct effects of group assignment on the incidence and severity of each complication (hypothesis 1), direct effects of group assignment on A1c (hypothesis 2), direct effects of A1c on the incidence and severity of microvascular complications (hypothesis 3), and the indirect effects of group assignment on the incidence and severity of each microvascular complication with A1 as a mediator of that relationship (hypothesis 4). The multiple mediator model answers all four hypotheses regarding the relationship between A1c, microvascular complications, and depressive symptomatology by providing direct effects of A1c on depressive symptomatology (hypothesis 1), direct effects of A1c on diabetes complications (hypothesis 2), direct effects of diabetes complications on depressive symptomatology (hypothesis 3), and specific and total indirect effects of A1c on depressive symptomatology with diabetes complications as mediators of that relationship (hypothesis 4).

Table 1

Participant Baseline Descriptive Characteristics and Demographic Information

Characteristic	Full Sample (N = 1441)	Primary Cohort (n = 726)	Secondary Cohort (n = 715)
	M (*SD*)	*M* (*SD*)	*M* (*SD*)
Age[a]	27.09 (7.11)	26.67 (7.41)	27.51 (6.78)
Education[a]	14.09 (2.28)	13.92 (2.43)	14.26 (2.11)
Diabetes duration[b]	69.78 (49.67)	33.46 (16.39)	106.65 (44.72)
A1c	8.89 (1.59)	8.82 (1.67)	8.97 (1.50)
Retinopathy	2.18 (1.57	1 (0.00)	3.38 (1.44)
Albumin Excretion Rate	15.93 (18.76)	11.82 (8.29)	20.10 (24.60)
Neuropathy	2.59 (.65)	2.70 (.56)	2.48 (.72)
Depression	5.32 (5.05)	5.54 (5.27)	5.10 (4.81)
	N (%)	*N* (%)	*N* (%)
Male gender	761 (52.8)	378 (52.1)	383 (53.6)
Married	706 (49.0)	351 (48.3)	355 (49.7)
White race	1391 (96.5)	698 (96.1)	693 (96.9)
Current smoker	304 (21.1)	145 (20.0)	159 (22.2)
Intensive treatment group	711 (49.3)	348 (47.9)	363 (50.8)

Note.[a] = in years. [b] = in months.

Table 2
Diabetes Control and Complications Trial Neurologic End Point Definitions

Category	Definition
Confirmed clinical neuropathy	A finding of definite clinical neuropathy by physical examination and history confirmed by unequivocal abnormality of either nerve conduction or autonomic nervous system response as defined below
Clinical neuropathy	A definite diagnosis of peripheral diabetic neuropathy by clinical examination based on the presence of at least two of the following: Physical symptoms Abnormalities on sensory examination Absent or decreased deep-tendon reflexes
Abnormal nerve conduction	At least one abnormal conduction attribute on each of at least two anatomically distinct peripheral nerves according to the following standards: Median motor nerve: Amplitude < 4.2 mV; Conduction velocity < 49.0 m/sec; F-wave latency > 31.8 m/sec Median sensory nerve: Amplitude < 10.0 μV; Conduction velocity < 48.0 m/sec; Peroneal nerve: Amplitude < 2.5 mV; Conduction velocity < 40.0 m/sec; F-wave latency > 56.0 m/sec Sural nerve: Amplitude <5.0 μV; Conduction velocity < 40.0 m/sec
Abnormal autonomic response	Any of the following indications of cardiac autonomic neuropathy: R-R variation (mean resultant) < 15.0 R-R variation < 20.0 in combination with Valsalva ratio < 1.5 Orthostatic hypotension caused by autonomic neuropathy as indicated by a decrease of at least 10 mm Hg in diastolic blood pressure in postural studies confirmed by blunted norepinephrine response in plasma catecholamine specimens
Subclinical neuropathy	Abnormal nerve conduction, autonomic nervous system response, or both without a definite diagnosis of peripheral neuropathy by clinical examination

Note. From: DCCT Research Group (1995a). The effect of intensive diabetes therapy on the development and progression of neuropathy. *Annals of Internal Medicine, 122,* 561-568.

Table 3

Abbreviated Summary of the Final Version of the Early Treatment Diabetic Retinopathy Study Scale of Diabetic Retinopathy Severity for Individual Eyes

Scale	Level	Severity	Definition
1	10	No retinopathy	Diabetic retinopathy absent
2	20	Very mild NPDR	Microaneurysms only
3	35	Mild NPDR	Microaneurysms plus hard exudates, cotton-wool spots, and/or mild retinal hemorrhages
4	43	Moderate NPDR	Microaneurysms plus mild IRMA or moderate retinal hemorrhages
5	47	Moderate NPDR	More extensive IRMA, severe retinal hemorrhages, or venous beading in one quadrant only
6	53	Severe NPDR	Severe retinal hemorrhages in four quadrants, or venous beading in at least two quadrants, or moderately severe IRMA in at least one quadrant
7	61	Mild PDR	NVE <0.5 disc area in one or more quadrants
8	65	Moderate PDR	NVE ≥0.5 disc area in one or more quadrants or NVD <0.25-0.33 disc area
9	71-75	High-risk PDR	NVD≥0.25-0.33 disc area and/or vitreous hemorrhage
10	81-85	Advanced PDR	Fundus partially obscured

Note. NPDR = nonproliferative diabetic retinopathy; IRMA = intraretinal microvascular abnormalities; PDR = proliferative diabetic retinopathy; NVE = new vessels elsewhere; NVD = new vessels on or within 1 disc diameter of optic disc.

Table 4

Abbreviated Final Version of the Early Treatment Diabetic Retinopathy Study Scale of Diabetic Retinopathy Severity for Persons

Step	Level (Worse Eye/Better Eye)
1	10/10
2	20/<20
3	20/20
4	35/<35
5	35/35
6	43/<43
7	43/43
8	47/<47
9	47/47
10	53/<53
11	53/53
12-23	≥61/<61

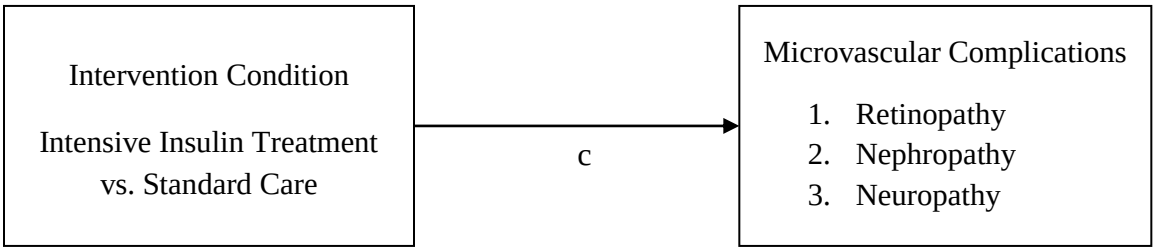
Table 5

Diabetes Control and Complications Trial Scale of Nephropathy

Level	Description
1	AER < 40mg/24hrs
1a	AER < 15 mg/24hrs
1b	15 ≤ AER < 40 mg/24rs
2	40 ≤ AER < 100 mg/24hrs
3	100 ≤ AER < 200 mg/24hrs
4	200 ≤ AER < 300 mg/24hrs
5	AER ≥ 300 mg/24hrs and Creatinine Clearance ≥ 70 ml/min/1.73m2
6	AER ≥ 300 mg/24hrs and Creatinine Clearance < 70 ml/min/1.73m2

Note. AER = Albumin excretion rate.

Direct Effects



Indirect Effects

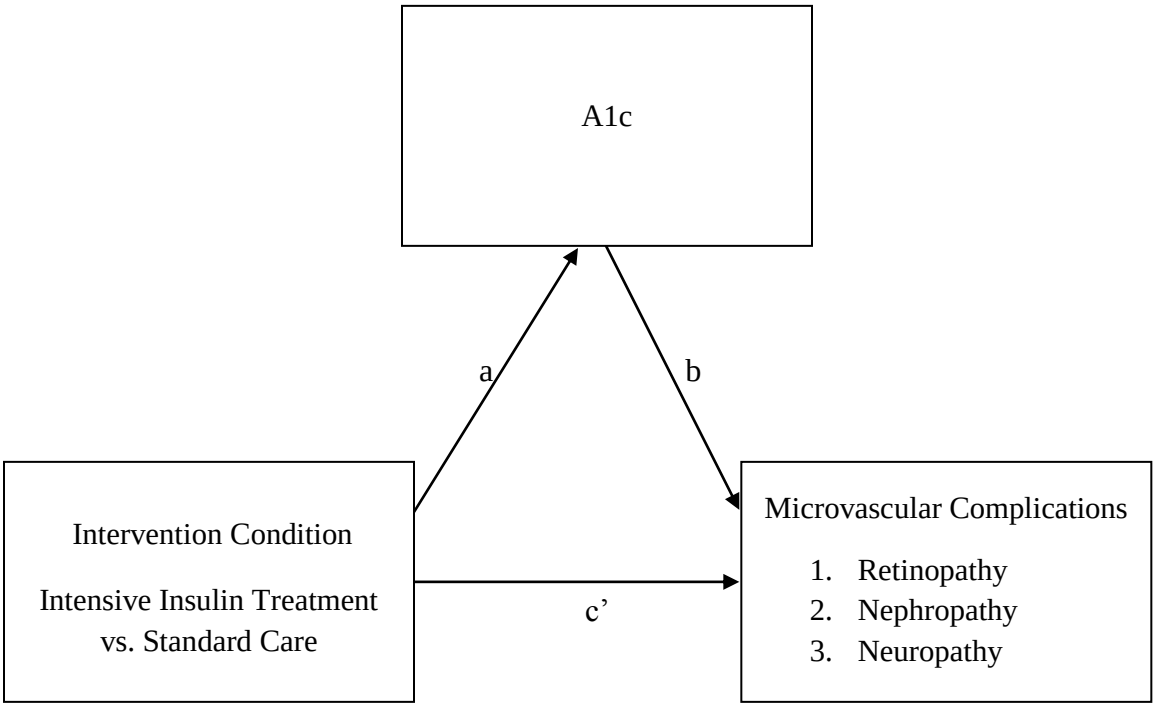
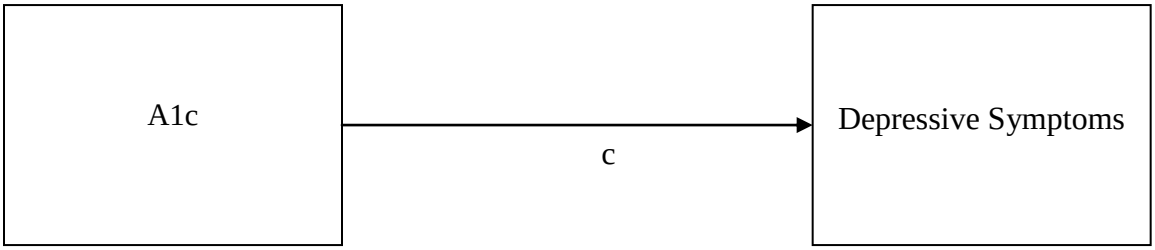


Figure 1. Graphical representation of the hypothesized simple-mediator model of DCCT intervention treatment condition, A1c, and microvascular diabetes complications. Three individual models with each microvascular complication as the dependent variable will be tested.

Direct Effects



Indirect Effects

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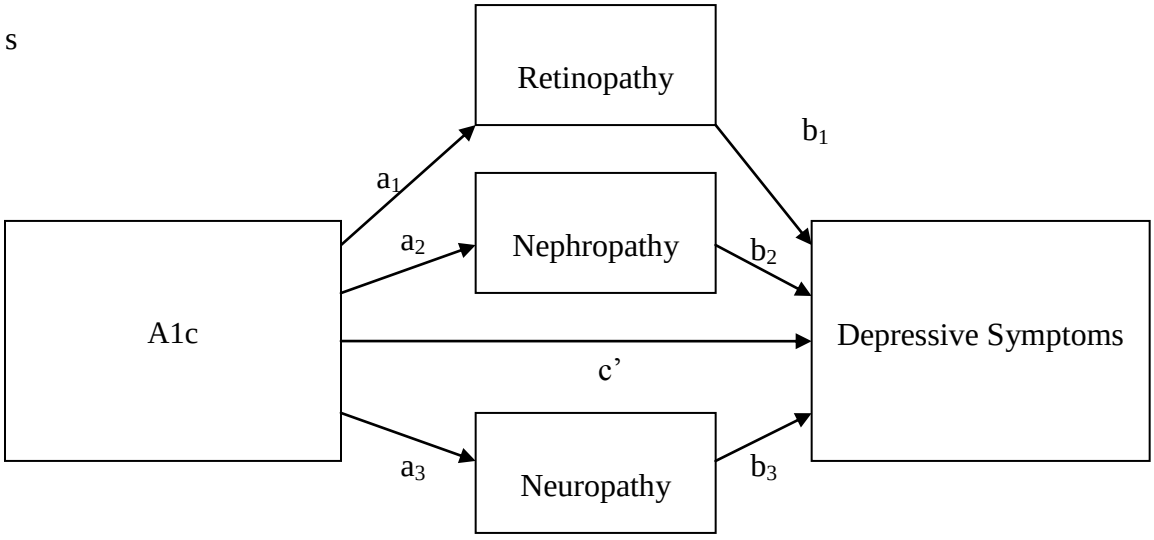


Figure 2. Graphical representation of the hypothesized multiple-mediator model of A1c, microvascular diabetes complications, and depressive symptomatology.

Results

Descriptives, t-tests, and Correlational Analyses

Mean values and standard deviations for average A1c between quarterly visits 4 through 12, average retinopathy, nephropathy, and neuropathy levels between quarterly visits 16 through 21, and average depressive symptomatology levels between quarterly visit 23 and 28 are presented in Table 6. Values are presented for the full DCCT sample and the primary and secondary intervention cohorts separately. Group comparisons showed that participants in the primary intervention group had lower levels of retinopathy, nephropathy, and neuropathy than participants in the secondary intervention cohort ($t(952.61) = -21.98$, $p < .001$, $d = .51$, $t(891.05) = -7.02$, $p < .001$, $d = .37$, $t(1220.56) = 4.57$, $p < .001$, $d = .27$, respectively), as expected. Average A1c levels were higher in the primary intervention cohort than the secondary intervention cohort ($t(1432.52) = 2.07$, $p < .05$, $d = .11$) and there was no difference in average depression levels between the primary and secondary intervention cohorts ($t(807) = 1.65$, n.s., $d = .12$).

Additionally, Pearson product-moment correlations between A1c, microvascular complications, and depressive symptomatolgoy and point-biserial correlations between these variables and DCCT treatment group assignment (standard vs. intensive treatment) are presented in table 6 for the full sample, primary intervention cohort, and secondary intervention cohort. As expected, A1c was significantly related to DCCT treatment group assignment and all microvascular complications in the expected direction in the full

sample as well as in both the primary and secondary intervention cohorts. Additionally, the microvascular complications were all significantly correlated in all samples. A1c was significantly related to depression in the full sample and the secondary intervention cohort, but not in the primary intervention cohort. DCCT treatment group assignment was significantly related to all variables except depression in the full sample and primary intervention group. Treatment group assignment and depression were significantly related in the secondary intervention group, however. Depressive symptomatology level was significantly related to neuropathy in the full sample and retinopathy and neuropathy in the secondary intervention cohort, but was not significantly correlated to any microvascular complications in the primary intervention cohort.

Single Mediation Models Analyses

Three proposed simple mediation models, illustrated in Figure 1, included A1c as a mediating variable in the relationship between DCCT treatment group assignment and retinopathy, nephropathy, and neuropathy. These three mediation models were tested for the full DCCT sample as well as for the primary and secondary intervention cohorts separately, resulting in a total of nine models. Age, gender, duration of diabetes, smoking status, and baseline values of A1c, depressive symptomatology, and microvascular complications were entered as covariates to control for their possible effects in each model. Retinopathy was omitted as a covariate for the primary intervention cohort model. It was predicted that DCCT treatment group assignment would be related to the presence and severity of each microvascular complication and that A1c would mediate these relationships.

To test for the significance of the mediation effect the Preacher and Hayes (2008) method of calculating standard errors and confidence intervals was used with 5,000 bootstrap samples used to estimate the bias corrected and accelerated confidence intervals. Results of these analyses can are summarized in Table 7. The total effect of DCCT intervention group on the severity of microvascular complications was significant for all three complications in the full sample as well as in the primary and secondary intervention cohorts. Indirect effects were significant for all of the models tested except for the model testing the meditational role of A1c on the relationship between DCCT treatment group and nephropathy in the primary intervention cohort. With inclusion of A1c as a mediating variable, the direct effect of DCCT group assignment on microvascular complications was nonsignificant for all models tested. This suggests that, with one exception of nephropathy in the primary intervention cohort, there is a significant mediation effect of DCCT treatment group assignment on microvascular complications through A1c, and A1c fully mediates the relationship between DCCT group assignment and microvascular complications. The full models, including DCCT treatment group assignment, A1c, and all covariates, accounted for a significant proportion of the variance ($p < .001$) in microvascular complication levels for all models tested. These results provide evidence for the assumption that the differences in the severity of microvascular complications seen in the DCCT are in fact due to differences in A1c resulting from the differences in treatment.

Multiple Mediation Models Analyses

A proposed multiple mediation model, illustrated in Figure 2, included retinopathy, nephropathy, and neuropathy as mediating variables in the relationship

between A1c and level of depressive symptomatology. The multiple mediator model was tested for the full DCCT sample as well as for the primary and secondary intervention cohorts separately, resulting in a total of three multiple mediator models. Age, gender, duration of diabetes, smoking status, and baseline values of A1c, depressive symptomatology, and microvascular complications were entered as covariates to control for their possible effects in each model. Because participants in the primary intervention cohort had no baseline retinopathy, retinopathy was omitted as a covariate for the primary intervention cohort model. It was predicted that A1c would be positively related to depressive symptomatology and that the severity of microvascular complications would mediate this relationship. Multiple mediator models in which all of the microvascular complications were entered simultaneously allowed for investigation of the total indirect effect of microvascular complications on the relationship between A1c and depressive symptomatology as well as the specific indirect effects of each of the individual complications while controlling for the other complications.

Results of the tests of multiple mediators for the full DCCT sample, the primary intervention cohort, and the secondary intervention cohort can be found in Figure 3, Figure 4, and Figure 5, respectively. In both the full DCCT sample and the secondary intervention cohort, total effects (*c)* indicated significant and substantial relations between A1c and depressive symptomatology levels. However, the total effect of the relationship between A1c and depressive symptomatology was not significant in the primary prevention cohort.

To test for the significance of the mediation effect the Preacher and Hayes (2008) method was used with 5,000 bootstrap samples used to estimate the bias corrected and

accelerated confidence intervals. Significance tests of the mediation effects can be found in Table 8. Total indirect effects were significant for the full DCCT sample as well as for the secondary intervention cohort. For the full DCCT sample, both nephropathy and neuropathy had significant ($p < .05$) specific indirect effects on the relationship between A1c and depressive symptomatology. None of the specific indirect effects, however, were significant for the primary intervention or secondary intervention cohorts. Contrasts of specific indirect effects were examined and all pairwise contrasts of indirect effects were nonsignificant, indicating that the magnitude of the specific indirect effects of the different microvascular complications could not be distinguished from one another in any of the models tested.

Despite significant mediation, the direct effects (*c'*) remained significant in both the full DCCT sample and the secondary intervention cohort, although the strength of the relationship was attenuated, suggesting that the presence and severity of microvascular complications partially mediates the relationship between A1c and depressive symptomatology in these samples. Total effects, mediation effects, and direct effects were all nonsignificant in the primary intervention cohort. The full models, including A1c, the three microvascular complications, and all covariates, accounted for a significant proportion of the variance ($p < .001$) in depressive symptomatology levels for all models tested. The models explained 18, 14, and 22 percent of the variance in depressive symptomatology levels for the full sample, primary intervention cohort, and secondary intervention cohort, respectively.

Table 6

Descriptive Statistics and Correlations of Average A1c, Retinopathy, Nephropathy, Neuropathy, and Depressive Symptomatology Levels.

Sample		1	2	3	4	5	*M*	*SD*	*N*
Full[a]	1. A1c average	—					8.17	1.57	1440
	2. Retinopathy	.24**	—				3.25	2.39	1359
	3. Nephropathy	.18**	.35**	—			1.17	.61	1419
	4. Neuropathy	-.16**	-.21**	-.15**	—		2.42	.76	1240
	5. Depression	.11**	.03	.06	-.12**	—	5.17	6.10	809
	6. DCCT Group	-.62**	-.16**	-.09**	.13**	-.06	—	—	1441
Primary[b]	1. A1c average	—					8.25	1.63	726
	2. Retinopathy	.45**	—				2.01	1.11	657
	3. Nephropathy	.16**	.18**	—			1.06	.30	716
	4. Neuropathy	-.17**	-.13**	-.09*	—		2.53	.71	554
	5. Depression	-.02	-.05	.03	-.11	—	5.62	6.22	310
	6. DCCT Group	-.65**	-.24**	-.09*	.15**	.03	—	—	726
Secondary[c]	1. A1c average	—					8.08	1.50	714
	2. Retinopathy	.31**	—				4.41	2.66	702
	3. Nephropathy	.23**	.32**	—			1.28	.79	703
	4. Neuropathy	-.18**	-.20**	-.16**	—		2.33	.79	686
	5. Depression	.19**	.10*	.08	-.15**	—	4.89	6.02	499
	6. DCCT Group	-.58**	-.20**	-.11**	.13**	-.11*	—	—	715

Note. * $p < .01$. ** $p < .001$. Average A1c values calculated between quarterly visits (QV) 4-12.
Average retinopathy, nephropathy, and neuropathy values calculated between QV 16-21.
Average depressive symptomatology levels between QV 23-28.
[a] = *n*s for correlations range from 777 – 1419. [b] = *n*s for correlations range from 297 – 716. [c] = *n*s for correlations range from 480 – 704.

Table 7

Mediation of the Effect of DCCT Treatment Group on Microvascular Complications through A1c for the full DCCT Group, and the Primary and Secondary Intervention Cohorts.

	Dependent Variable (DV)	Effect of IV on M (*a*)	Effect of M on DV (*b*)	Total Effect (*c*)	Indirect Effect (*ab*) (*SE*)	Indirect Effect 95% CI	Direct Effect (*c'*)	R^2
Full	Retinopathy[a]	-1.93***	.33***	-.73***	-.63* (.10)	[-.83, -.44]	-.10	.58***
	Nephropathy[b]	-1.95***	.05***	-.11***	-.11* (.03)	[-.18, -.05]	-.0004	.21***
	Neuropathy[c]	-1.92***	-.09***	.21***	.16* (.04)	[.09, .24]	.05	.20***
Primary	Retinopathy[d]	-2.07***	.20***	-.52***	-.42* (.10)	[-.62, -.25]	-.10	.33***
	Nephropathy[e]	-2.11***	.01	-.06**	-.03 (.02)	[-.07, .003]	-.03	.09***
	Neuropathy[f]	-2.07***	-.07*	.21***	.15* (.06)	[.03, .27]	.06	.15***
Secondary	Retinopathy[g]	-1.78***	.45***	-.92***	-.80* (.16)	[-1.14, -.50]	-.12	.49***
	Nephropathy[h]	-1.79***	.10***	-.17**	-.18* (.06)	[-.32, -.08]	.01	.24***
	Neuropathy[i]	-1.79***	-.10***	.21***	.18* (.05)	[.08, .28]	.03	.22***

Note. * $p < .05$. ** $p < .01$. *** $p < .001$. All coefficients represent point estimates while controlling for gender, age, diabetes duration, smoking status, and baseline values of A1c, depressive symptomatology, and microvascular complications.
[a] $n = 1347$. [b] $n = 1407$. [c] $n = 1232$. [d] $n = 652$. [e] $n = 711$. [f] $n = 552$. [g] $n = 695$. [h] $n = 696$. [i] $n = 680$.

Table 8

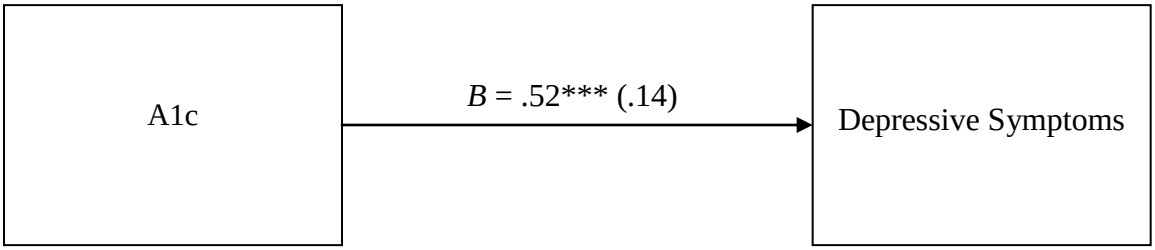
Mediation of the effect of A1c on depressive symptomatology through the microvascular complications of retinopathy, nephropathy, and neuropathy in the full DCCT participant cohort, primary prevention cohort, and secondary intervention cohort.

Mediators	Full DCCT Cohort[a]		Primary Prevention Cohort[b]		Secondary Intervention Cohort[c]	
	Indirect Effects Coefficient (*SE*)	Bootstrapping 95% CI	Indirect Effects Coefficient (*SE*)	Bootstrapping 95% CI	Indirect Effects Coefficient (*SE*)	Bootstrapping 95% CI
Total mediated effect	.19* (.07)	[.06, .34]	.03 (.10)	[-.15, .27]	.22* (.09)	[.06, .43]
Retinopathy	.06 (.05)	[-.02, .17]	-.06 (.07)	[-.23, .05]	.11 (.07)	[-.01, .27]
Nephropathy	.05* (.03)	[.0001, .12]	.01 (.03)	[-.03,.13]	.05 (.05)	[-.02, .16]
Neuropathy	.08* (.04)	[.01, .18]	.08 (.07)	[-.02, .27]	.06 (.05)	[-.02, .18]

Note. *$p < .05$ as determined by the 95% bias corrected and accelerated bootstrapping confidence interval (CI). All coefficients represent point estimates while controlling for gender, age, diabetes duration, smoking status, and baseline values of A1c, depressive symptomatology, and microvascular complications.

[a]$n = 766$, [b]$n = 295$, [c]$n = 471$.

Direct Effects



Indirect Effects

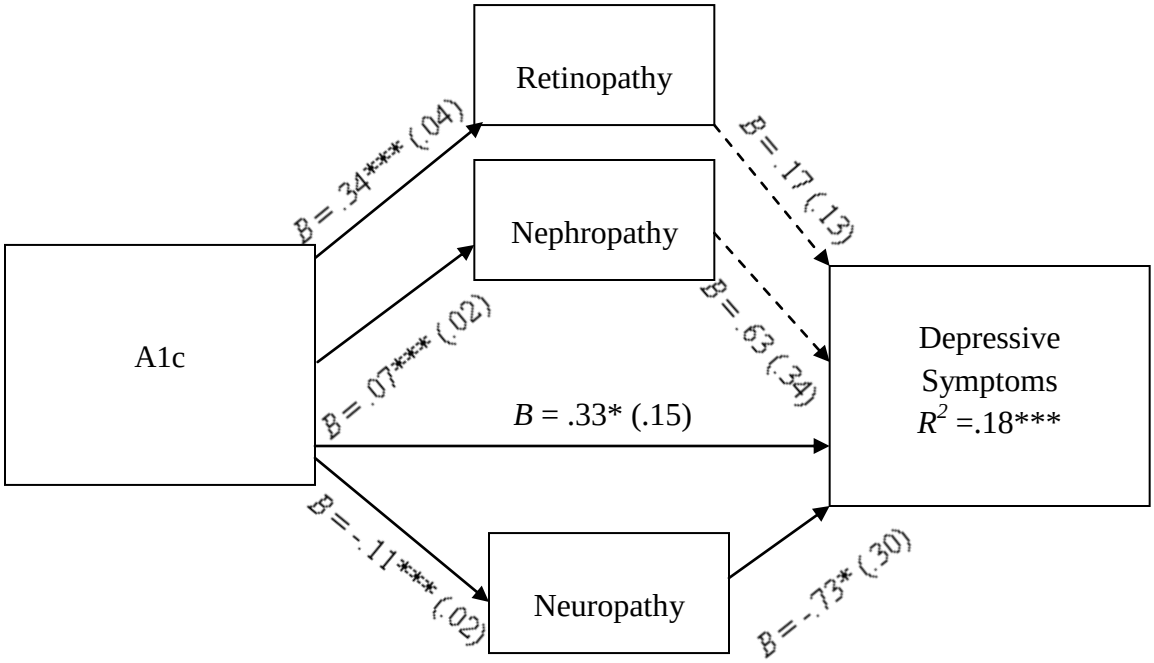
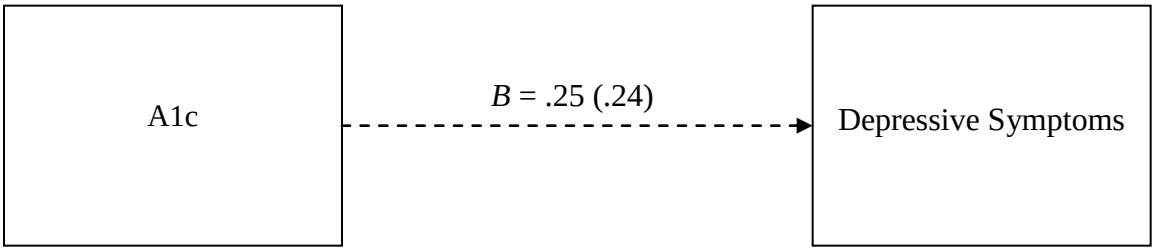


Figure 3. Multiple mediation test of the role of microvascular complications in the relationship between A1c and depressive symptomatology for the full DCCT sample. All coefficients represent unstandardized regression coefficients (*Standard Error*) while controlling for age, gender, diabetes duration, smoking status, and baseline levels of A1c, depression, and microvascular complications.

Direct Effects



Indirect Effects

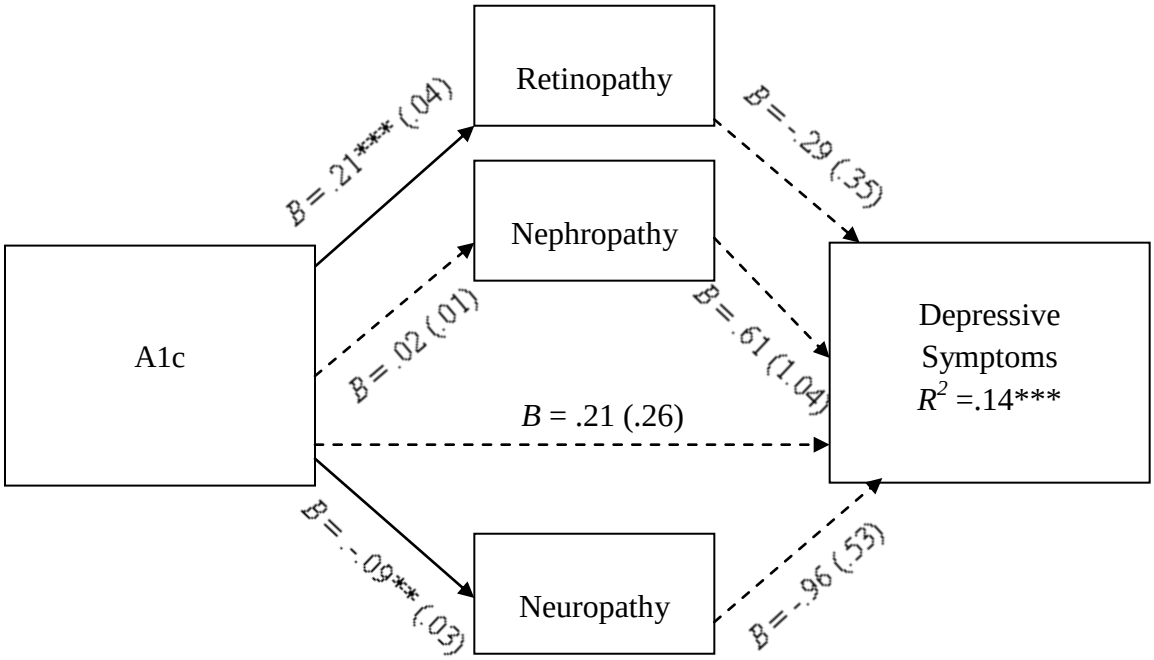
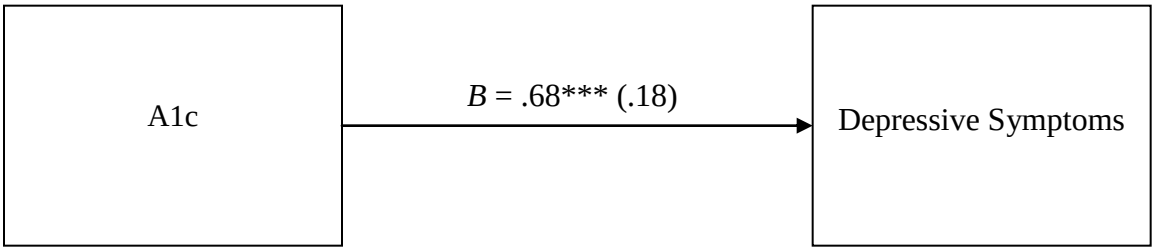


Figure 4. Multiple mediation test of the role of microvascular complications in the relationship between A1c and depressive symptomatology for the primary prevention cohort of the DCCT. All coefficients represent unstandardized regression coefficients (*standard error)* while controlling for age, gender, diabetes duration, smoking status, and baseline levels of A1c, depression, and microvascular complications.

Direct Effects



Indirect Effects

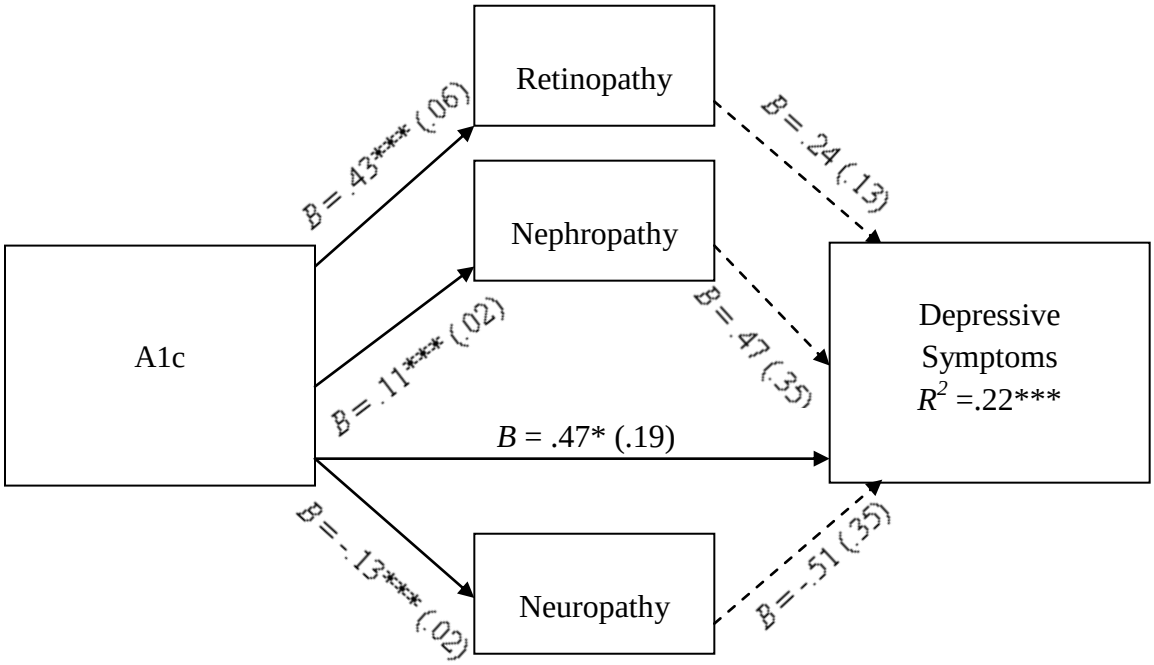


Figure 5. Multiple mediation test of the role of microvascular complications in the relationship between A1c and depressive symptomatology for the secondary intervention cohort of the DCCT. All coefficients represent unstandardized regression coefficients (*standard error)* while controlling for age, gender, diabetes duration, smoking status, and baseline levels of A1c, depression, and microvascular complications.

Discussion

The Relationship Between A1c, Complications, and Depressive Symptoms

The current study examined the relationship between A1c, microvascular complications, and depressive symptomatology in people with type 1 diabetes. The DCCT data set was used to examine these relationships because it provides longitudinal data which enhances our understanding of the temporal sequence involved in these relationships. Results from preliminary analyses were consistent with hypotheses, as A1c fully explained the relationship between DCCT treatment group and the severity of three microvascular complications: retinopathy, neuropathy, and nephropathy. The primary goal of the study was to determine if the severity of these microvascular complications explained the relationship between A1c and depressive symptoms. Consistent with hypotheses, the severity of microvascular complications helps to explain the relationship between A1c and depressive symptoms. The severity of microvascular complications partially mediated the relationship between A1c and depressive symptoms for the full sample as well as for a secondary intervention subset of participants who began the study with early stage levels of retinopathy. However, in the primary prevention cohort whose members had no baseline retinopathy, A1c was not predictive of depressive symptomatology levels, and microvascular complications did not mediate the relationship between A1c and depressive symptoms. For the full sample, the A1c-depressive symptoms relationship was explained in part by the combined effect of all three microvascular complications. However, further analyses indicated that the combined

effect was primarily due to specific indirect effects of nephropathy and neuropathy (but not retinopathy). Additionally, in the secondary intervention cohort, the A1c-depressive symptoms relationship was explained in part by the combined effect of all three microvascular complications, but not by specific effects of the individual microvascular complications. These results provide support for diabetic complications as one explanation of the relationship between A1c and depressive symptoms, specifically in later stages of the diabetes disease process when microvascular complications become more severe.

The results of the present study suggest that microvascular complications of diabetes significantly contribute to depressive symptom levels and explain the relationship between A1c, both a measure of glycemic levels over time as well as an index of success in the self-management of diabetes, and depression levels. These findings are consistent with a consequence model of diabetes and depression, which suggests that depressive symptoms result as a consequence of medical problems that occur as a result of poor glycemic control (W. P. Sacco, et al., 2007; W. P. Sacco, et al., 2005). The antecedent theory of depression in diabetes, which suggests that medical problems arise as a result of depression leading to decreased self-management and increased A1c, may be a reasonable alternative or even a complement to the consequent model; i.e., a bidirectional model is plausible. However, the longitudinal nature of the current models tested provides evidence for the hypothesized temporal relationship between A1c, diabetes related complications, and depressive symptom levels. This temporal evidence lends further support for the consequence model of the development of

depression in people with diabetes and its relation to A1c and associated medical problems.

Additionally, the results suggest that the explanatory role of microvascular complications in the relationship between A1c and depression tends to be most evident for people with more severe diabetic complications. Results for the full sample were driven by the secondary cohort, which was comprised of people with significantly higher baseline levels of retinopathy, longer diabetes disease duration, and, therefore, longer exposure to hyperglycemia than their primary cohort counterparts. The difference in the role of microvascular complications in the relationship between A1c and depressive symptoms for the cohorts may be reflective of these differences. Microvascular complications tend to develop and progress with longer disease duration (Fong, et al., 2004; Luk, et al., 2008; Moss, Klein, & Klein, 1992; Orchard, et al., 1990), and are often asymptomatic at early stages (Boulton, et al., 2005; Fong, et al., 2004; Soldo, Brkljacic, Bozikov, Drinkovic, & Hauser, 1997). Based on these trends, the detrimental effects of microvascular complications on psychological health are perhaps not evident until the complications are sufficiently severe enough to be symptomatic. The symptoms of these diabetes complications may be disruptive through pain and functional impairment (W. P. Sacco, Bykowski, & Mayhew, 2010) that result with increasing severity of the complications, consequentially resulting in higher depressive symptom levels.

Strengths

These results are consistent with previous studies which have shown positive associations between A1c, depression, and microvascular complications (de Groot, Anderson, Freedland, Clouse, & Lustman, 2001; Lustman, et al., 2000). Similarly, results

are consistent with the few previous longitudinal studies of A1c and depressive symptoms available. Longitudinal analysis of A1c and depressive symptoms in people with type 2 diabetes suggest that poor glycemic control can increase risk of depressive symptoms for people with intensive (i.e., insulin) treatment regimen, but not those on oral medication alone (Aikens, Perkins, Lipton, & Piette, 2009). An additional longitudinal investigation shows a positive relationship between A1c and depression over time, but the nature of the data precludes causal inferences (Richardson, Egede, Mueller, Echols, & Gebregziabher, 2008). However, most studies use cross-sectional data which severely limits the conclusions that can be drawn from the results. Furthermore, no previous studies have examined the interrelationship among these variables in a single model using longitudinal experimental data, as the current study does, which provides evidence of a temporal relationship between the variables. The present study also adds to the existing body of research by providing a comprehensive theoretically based model of the relationship between these variables over time providing evidence for the depression as consequence model of diabetes. Additionally, the present study has the advantage of using objective biological markers in the measurement of the microvascular complications, including nerve conduction studies for neuropathy and albumin excretion rates for nephropathy, thus providing more concrete and accurate measurements of the symptom severity without relying on potentially inaccurate subjective self-reports or global clinical judgments.

Additionally, a multiple mediator model with bootstrapping was used to investigate the role of microvascular complications in the relationship between glycemic control and depressive symptomatology. This is a superior method of analysis than single

mediator models because it provides information of the total mediation effect of the microvascular complications, accounting for their intercorrelation, as well as specific indirect effects of each individual complication while controlling for the others. The analyses also statistically controlled for factors that are known to be associated with microvascular complications and depressive symptomatology. By controlling for baseline levels of variables included in the model as well as possible demographic confounds, the effects of A1c on depression and the meditational role of complications in this relationship could be identified independent of the known potential confounds.

Clinical Implications

The role of A1c and microvascular complications in the development of depressive symptomatology is an important factor to consider for clinical interventions. Because the relationship between A1c, microvascular complications, and depression may not be evident until later in the diabetes disease process, prevention of later psychological issues related to the disease should be focused on through an emphasis on effective disease management early on in the disease process. Diabetes self-management programs are considered a critical element of care for people with diabetes, as they have been found to be effective in improving glycemic control (Ellis, et al., 2004; Funnell, et al., 2009; Norris, Lau, Smith, Schmid, & Engelgau, 2002). Addressing related psychosocial issues is recommended as core components of self-management curriculum in addition to diabetes-specific behavioral and medical considerations (Funnell, et al., 2009). In light of the current findings it is recommended that diabetes self-management interventionists be especially vigilant about the psychological effects, particularly depression, of medical complications associated with diabetes. Consideration of these associations should be

given not only for the psychological health of people with diabetes, but also because the relationship between diabetes and depression may very well be bidirectional, and depression is likely to interfere with adherence to diabetes self-management regimens (Gonzalez, et al., 2008).

Limitations

Some caveats should be noted. First, the current study was based on a long-term clinical research trial with a well-educated largely white sample of people with type 1 diabetes. It is possible that clinical trials, which generally require participants follow fairly strict protocol regulations, attract a unique group of participants with characteristics that differ in significant ways from the general population. Furthermore, the homogeneity of race and educational levels in the current sample limits the applicability of the findings to the larger population. It is also possible that the relationships gleaned in the current study of people with type 1 diabetes may manifest somewhat differently in people with type 2 diabetes. Given that the overwhelming majority of cases of diabetes are type 2, it would be useful to test the applicability of the current models in a type 2 diabetes population. Furthermore, differences in sample size between the primary and secondary intervention cohorts may contribute to differences in power and, therefore, the ability to detect significant relationships between the variables in the mediation models. Further testing of these models in comparably sized samples of people with diabetes with varying stages of the disease and varying severities of complications should be tested. Additionally, despite using longitudinal experimental data, testing for mechanisms of the proposed relationship between A1c and depressive symptoms, and controlling for known variables that can influence the variables investigated, the possibility of a third

unmeasured variable accounting for the present relationships remains. Potential confounding variables such as self-management and adherence among others should be considered in future investigations.

Future Directions

Continued exploration of the applicability of the current findings in a more heterogeneous sample including greater variability in educational attainment levels and racial and ethnic backgrounds in a longitudinal fashion would be prudent. Additionally, the models of the interrelationships between the A1c, microvascular complications, and depressive symptoms should be investigated in people with type 2 diabetes. Furthermore, future studies should investigate the mechanisms through which microvascular complications contribute to depressive symptomatology levels, such as by contributing to loss of reinforcement through pain and functional limitation.

Conclusion

In summary, A1c mediated the relationship between DCCT group assignment and the severity of the diabetes related microvascular complications of retinopathy, nephropathy, and neuropathy. Furthermore, A1c was related to depressive symptom levels in the full sample and the secondary cohort, and this relationship was explained, in part, by the severity of microvascular complications. Longitudinal analyses provide evidence for the temporal relationship between these variables. These results are consistent with the depression-as-consequence-model of depression, which proposes that depression occurs as a result of medical symptoms and complications that occur from poor diabetes self-management and poorly controlled glycemic levels. However, these

relationships may not be evident until later in the disease process when complications become increasingly severe and problematic.

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Appendix A:

Symptom Checklist-90-Revised Depression Dimension Subscale

Symptom Checklist-90-Revised Depression Dimension Subscale

Instructions: Below is a list of problems people sometimes have. Please read each one carefully, and blacken the circle that best describes HOW MUCH THAT PROBLEM HAS DISTRESSED OR BOTHERED YOU DURING THE PAST 7 DAYS INCLUDING TODAY. Blacken the circle for only one number for each problem and do not skip any items. If you change your mind erase your first mark carefully.

"Number" refers to the following descriptor phrases:

0 = Not at all; 1 = A Little bit; 2 = Moderately; 3 = Quite a Bit; 4 = Extremely

Item	0	1	2	3	4
5. Loss of sexual interest or pleasure	○	○	○	○	○
14. Feeling low in energy or slowed down	○	○	○	○	○
15. Thoughts of ending your life	○	○	○	○	○
20. Crying easily	○	○	○	○	○
22. Feelings of being trapped or caught	○	○	○	○	○
26. Blaming yourself for things	○	○	○	○	○
29. Feeling lonely	○	○	○	○	○
30. Feeling blue	○	○	○	○	○
31. Worrying too much about things	○	○	○	○	○
32. Feeling no interest in things	○	○	○	○	○
54. Feeling hopeless about the future	○	○	○	○	○
71. Feeling everything is an effort	○	○	○	○	○
79. Feelings of worthlessness	○	○	○	○	○

Appendix B:

Neuropathy Measurement Definition

Neuropathy Measurement Definition

Nerve conduction of the dominant median (motor and sensory), peroneal (motor), and sural nerves was evaluated using standard techniques and stimulation-to-recording electrode distances or specified anatomical landmarks. A standardized physical and neurologic history was completed by DCCT neurologists at baseline, 5 years, and at study end. Peripheral, somatic, and autonomic neuropathic symptoms were investigated during the neurological examination. Deep-tendon reflexes and peripheral sensation including light touch, pin-prick, temperature, and position, were measured during the physical exam. Clinical neuropathy was indicated by abnormal findings in any two categories of neuropathic symptoms, sensory deficits, or impaired reflexes. Confirmed clinical neuropathy was defined as clinical neuropathy determined by a definite abnormal neurologic examination (defined by at least two of the following: sensory signs, absent or hypoactive reflexes consistent with distal symmetrical polyneuropathy, or positive responses among symptoms) confirmed by abnormal testing in either nerve conduction or autonomic nervous system testing or both (defined by a value above or below the absolute threshold of normal for amplitude, velocity of conduction, distal latency, or F-wave latency in at least two anatomically distinct nerves). Possible clinical neuropathy was defined as a participant with only one abnormal finding among symptoms sensory signs, or absent or hypoactive reflexes, regardless of the normality of nerve conduction study outcomes. Secondary outcome variables assessed included clinical neuropathy (defined as a peripheral diabetic neuropathy diagnosis based on the presence of at least two of the following: physical symptoms, abnormalities on sensory examination, and decreased or absent deep-tendon reflexes), subclinical neuropathy (as defined by either abnormal nerve conduction, abnormal autonomic nervous system response, or abnormalities in both of these measurements without a definite diagnosis of peripheral neuropathy by clinical examination), abnormal nerve conduction, and abnormal autonomic nervous system test results (DCCT Research Group, 1995a).