SCREENING FOR CHRONIC COMPLICATIONS IN TYPE 1 DIABETES

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Diabetes is associated with significant morbidity and mortality. The majority of disease burden is attributed to long-term complications. Screening tests to detect and therapies to treat early forms of diabetes complications are available, but few diabetes patients receive screening at the recommended levels.

This report investigated the prevalence and correlates of screening in a cohort of type 1 diabetes patients. The study population was the Pittsburgh Epidemiology of Diabetes Complications study cohort. Screening tests assessed included the HbA1c test, dilated eye exam, foot exam, fasting lipid profile, and urine protein screen. The aims were to: 1) identify the frequency and trends in screening; 2) identify general correlates of screening as well as to evaluate the influence of patient behavior and health care access factors on receipt of screening tests and examine the association between clinical risk of developing complications and receipt of screening tests to detect complications.

Reported screening rates varied widely between individual tests, and optimal screening, the use of all tests, was reported by the fewest subjects. Overall, screening in this population is improving over time. The strongest general correlates of screening were specialist care, weekly blood sugar testing, and gender. A more in depth analysis of screening predictors was aimed at determining whether patient or health care access level factors have a stronger influence on screening was conducted. Health care access factors that specifically included specialist care, intensive insulin therapy, and number of physician visits were found to have a stronger influence

on screening compared to patient level factors. Finally, this study found that overall, screening does not appear to be associated with clinical risk of developing complications.

Based upon this research, areas in need of improvement include optimal screening rates and targeting screening endeavors towards patients at clinical risk for developing complications, and interventions that incorporate access factors may have the strongest impact. The findings of this report have public health significance and have implications for diabetes preventive care. The data from this research can be used to design interventions and policies that improve screening rates, and reduce subsequent morbidity and mortality associated with chronic complications.

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1.0 Introduction

1.1 Overview

Diabetes is a significant public health problem. It is associated with many forms of burden and affects many members of the U.S. population. The natural history of diabetes leads to the development of chronic complications, including nephropathy, retinopathy, neuropathy, peripheral vascular disease, and cardiovascular disease. Screening tests for these complications and risk factors for these complications exist. Several reports have demonstrated that early detection and treatment of these conditions prevent their progression. This doctoral thesis will focus on screening for chronic diabetes-related complications, as it pertains to individuals with type 1 diabetes. The format of this thesis is as follows: 1) Description of the public health significance of diabetes and diabetes-related chronic complications; 2) Review of the screening literature; 3) Description of study aims and methods; 4) Research manuscripts and 5) Discussion of research findings.

1.2 Public Health Significance of Diabetes

Diabetes is one of the major chronic diseases affecting the U.S. population. Diabetes mellitus is a metabolic disorder diagnosed in a clinical setting by a high fasting plasma glucose level or a 2-hour plasma glucose level (Gerstein H. C. 2001). In 2005, an estimated 7.0% of the U.S. population (about 20.8 million) had diabetes (Centers for Disease Control and Prevention 2005). The National Health Interview Survey (NHIS) found a 4-8 fold increase over the last half century in the number of persons with a diagnosis of diabetes rising from 1.6 million in 1958 to 12.1 million in 2000, and the prevalence of diagnosed diabetes rose from .9% to 4.4% in this period (Centers for Disease Control and Prevention 2003; Centers for Disease Control and Prevention 2004a; Engelgau et al. 2004; Kenny S.J. 1995). Moreover, the U.S. Population is

projected to grow 17% between the year 2002 and 2020, but the diabetes population is projected to increase 44%(Engelgau et al. 2004).

There are two major forms of diabetes, type 1 and type 2 diabetes. Type 1 diabetes accounts for 5-10% of all diagnosed cases. It is a chronic disease characterized by hyperglycemia due to the absolute deficiency of insulin secretion. It is caused by the autoimmune destruction of pancreatic beta cells. It usually develops before 30 years of age, but can occur at any age (Lawson M 2001). Genetics play an important role in the development of type 1 diabetes. The most important genetic determinant is the histocompatibility locus (HLA), however type 1 diabetes is a polygenic disorder (Lawson M 2001). Other risk factors for type 1 diabetes have also been identified, including the consumption of cow's milk in childhood, caffeine, nitrites, and enterovirus infections during childhood (Hyoty et al. 1995; Virtanen et al. 1998). Children who have siblings with diabetes and drink more than 16 oz of milk per day during childhood have fourfold increased risk for developing disease (Virtanen et al. 1998). Enterovirus infections during childhood (coxsackie B) are associated with 5.7 fold increase in risk of developing type 1 diabetes (Hyoty et al. 1995). In 2005, about one in every 400 to 600 children and adolescents had type 1 diabetes in the United States, similar to the reported prevalence in 2003 (Centers for Disease Control and Prevention 2005). Overall, however, there is an increasing trend in the incidence of type 1 diabetes worldwide (Karvonen M 2001).

Type 2 diabetes accounts for 90-95% of all diagnosed cases of diabetes. It is a chronic disease characterized by insulin resistance. The development of type 2 diabetes depends on both hereditary and behavioral factors, and the prevalence varies among different ethnic groups. Risk factors for type 2 diabetes include age, obesity, ethnicity, family history of diabetes, gestational diabetes, low birth weight, sedentary lifestyle, higher systolic blood pressure, metabolic

syndrome, impaired glucose tolerance, and impaired fasting glucose (Capes S 2001). Up to one half of all cases of type 2 diabetes may be undiagnosed (Capes S 2001). Additionally, in the United States minority groups have higher rates of type 2 diabetes compared to whites: African-Americans are 1.6 times as likely, Hispanics are 1.5 times as likely and Native Americans are 2.2 times as likely to have type 2 diabetes compared to whites(Centers for Disease Control and Prevention 2004b).

Diabetes is associated with many adverse short term and long term complications. The main short term complications are hyperglycemia and hypoglycemia. Hyperglycemia refers to high blood sugar, and occurs when the body has too little insulin. It is extremely serious. Untreated hyperglycemia leads to ketoacidosis, a serious and potentially fatal complication. The age-adjusted hospital discharge rate for diabetic ketoacidosis in 2002 was 28.4 per 1,000 for males and 19.7 per 1,000 for women (Centers for Disease Control and Prevention 2004a). Hypoglycemia is low blood sugar, and happens from time to time to everyone who has diabetes. Unrecognized and untreated hypoglycemia may cause a loss of consciousness. Among persons with type 1 diabetes, patients suffer from hypoglycemic episodes on average two times per week. Hypoglycemia is attributable to an estimated 2-4% of deaths among persons with type 1 diabetes(Cryer 2002).

The overwhelming majority of diabetes morbidity and mortality is attributed to long term complications. Over 200,000 deaths per year are attributed to diabetes complications. The chronic conditions include diabetic eye disease from retinopathy, kidney disease from nephropathy, foot disease from neuropathy and peripheral vascular disease, and cardiovascular disease. Diabetes is the leading cause of kidney failure and new blindness in adults. More than 60% of nontraumatic leg and foot amputations are among diabetes patients. Diabetes is also a

major cause of heart disease and stroke, which account for about 65% of deaths among people with diabetes (Centers for Disease Control and Prevention 2004b).[11]

People with diabetes are hospitalized more frequently than those without the disease and use physician services at a higher rate than nondiabetic individuals (Aro et al. 1994; Harris 1998; Laditka et al. 2001; Rendell et al. 1993). Diabetes is associated with rates of lost work time, disability, and premature mortality(Centers for Disease Control and Prevention 2004a). In 2003, 33.6% of U. S adults with diabetes reported at least one day of poor mental health and 55.8% reported at least one day of poor physical health in the past 30 days (Centers for Disease Control and Prevention 2004a). In addition, 35.1% of adults with diabetes were unable to perform their usual activities at least one day in the month due to either poor mental or physical health (Centers for Disease Control and Prevention 2004a). In 2002, among adults with diabetes, 59.3% reported a mobility limitation which included walking a quarter of a mile, climbing 10 steps, standing for 2 hours, stooping, bending or kneeling (Centers for Disease Control and Prevention 2004a).

Diabetes is a very costly disease with a significant financial burden to patients as well as the U.S. economy. Diabetes cost the U.S. an estimated $132 billion in 2002 (Hogan et al. 2003). A total of $92 billion in direct medical expenditures were attributable to diabetes in 2002; with 23.2 billion resulting from costs related to diabetes care, 24.6 billion from chronic complications attributed to diabetes, and 44.1 billion resulting from costs related to the excess prevalence of general medical conditions. Indirect expenditures attributable to diabetes consisting of lost work days, restricted activity days, mortality, and permanent disability due to diabetes totaled 39.8 billion (Hogan et al. 2003). An estimated 176,475 person-years of permanent disability in 2002 are attributable to diabetes; each case of permanent disability results in an average lost earnings

of $42,462 per year (Hogan et al. 2003). Data from an employer-based insurance population showed that although diabetes patients comprised 1.6% of the population, they were responsible for 9.4% of costs (Hogan et al. 2003). Economic loss to the U.S. economy from diabetes is estimated to be 40 billion annually. Per capita medical expenditures totaled $13,243 for people with diabetes compared to $2,560 for people without diabetes (Hogan et al. 2003).

Screening for chronic diabetes-related complications to detect early forms of the disease is now widely available. The American Diabetes Association (ADA) recommends regular screening for diabetic eye, kidney and foot disease and risk factors for cardiovascular disease (American Diabetes Association 2005). Regular eye exams and timely treatment could prevent up to 60% of diabetes-related blindness (Centers for Disease Control and Prevention 2004b). Foot care programs that include regular examinations and patient education could prevent up to 85% of diabetes-related amputations (Centers for Disease Control and Prevention 2004b). Treatment and better control of blood pressure could reduce heart disease and stroke by up to 50% and diabetes-related renal failure by 33% (Centers for Disease Control and Prevention 2004b). Although screening has been show to be efficacious, not all diabetes patients receive the recommended levels of screening. This problem is the focus of this doctoral thesis. This research will examine the factors associated with screening for chronic complications. The goal of this work is to elucidate factors associated with screening for chronic complications in type 1 diabetes in an attempt to provide evidence from which interventions can be formed to improve early detection. This doctoral thesis will 1) Describe chronic diabetes-related complications; 2) Review the screening literature; 3) Describe the study aims and methods; 4) Provide three original research manuscripts related to screening and 5) Sum the research findings.

2.0 Chronic Complications

2.1 Introduction to Diabetes Complications

Diabetes is associated with several late-stage complications that lead to subsequent morbidity and mortality. These late-stage complications are generally categorized by the terms microvascular and macrovascular disease. Microvascular disease results from the impact of glucose intolerance on the smaller blood vessels and includes retinopathy, nephropathy and neuropathy. Macrovascular disease involves the larger vessels and is associated with atherosclerotic activity of these vessels, and includes cardiac, cerebral, and peripheral vascular disease (Group 1993; Wang et al. 1993). Late-stage complications are hypothesized to occur when diabetes and certain risk factors are not controlled as close to normal physiologic levels as possible. Higher blood sugar levels have been associated with these adverse health events (Nathan 1993). Late stage retinopathy, or diabetic eye disease, leads to vision loss. End-stage renal disease is the most severe stage of nephropathy, and results in significant levels of disability and premature death. Amputation is the end result of diabetic foot disease, and is often found in the presence of neuropathy and peripheral vascular disease. Coronary heart disease is a common macrovascular event in disease patients. These complications are influenced by the same risk factors, which include lack of glycemic control, hypertension, hyperlipidemia. Glycemic control is the major influence on the development of microvascular complications, while blood pressure and lipid control largely drive the development of macrovascular disease(Bate & Jerums 2003).

2.2 Diabetic Kidney Disease

Diabetic nephropathy is the leading known cause of end-stage renal disease (ESRD) in the United States, accounting for an estimated 28,000 new cases of ESRD per year. The majority of future ESRD cases from diabetic nephropathy are preventable (Skyler 2001). Diabetic nephropathy affects 20-30% of patients with type 1 diabetes, and develops about 20 years after diabetes is diagnosed. Although diabetes accounts for approximately 40% of ESRD in the U.S., diabetes patients consume 75% of ESRD costs. Less than 20% of diabetes patients with end-stage renal disease have a five year life expectancy (Skyler 2001).

The stages of nephropathy are described in Table 1 (Borch-Johnsen 2001; Jensen et al. 1993; Mogensen 1986). Nephropathy is defined as persistent proteinuria (more than 500 mg of protein or 300 mg of albumin/24 hours) in patients without urinary tract infection or other diseases that cause proteinuria (Mogensen 1986). In patients with type 1 diabetes, development of clinical nephropathy is a relatively late event; in type 2 diabetes, it may be present at diagnosis (Klein et al. 1984b). Patients with untreated proteinuria will develop end stage renal disease and die after 7-8 years (Andersen et al. 1983). In type 1 diabetes, patients with microalbuminuria have a substantial excess mortality rate compared to normoalbumuinuric patients (Deckert et al. 1996). For type 1 diabetes patients with clinical diabetic nephropathy, end-stage renal disease/uraemia is the dominating cause of death, responsible for nearly 60% of all deaths (Krolewski et al. 1985).

Table 1

Stages of Diabetic Nephropathy

Stage	Characteristics
Normal albumin excretion	The albumin excretion rate in non-diabetic individuals as well as patients with newly diagnosed type 1 diabetes is well below 30mg/24 hours. In non-diabetic individuals, the median albumin excretion rate is 2.3μgram/min.[8]
Microalbuminuria	Defined as urinary albumin excretion rate (UAER) between 30 and 300mg/24 hour (20-200 μg/min) in two out of three consecutive urine samples.[9] Individuals with microalbuminuria may have normal blood pressure. The prevalence in type 1 diabetes patients ranges from 9-20% and in type 2 diabetes patients ranges from 13-27%.[5]
Clinical diabetic nephropathy	Clinical diabetic nephropathy is defined as UAER exceeding 300mg/24 hour or total protein excretion exceeding .5g/24hour.[5] Individuals with clinical diabetic nephropathy have elevated blood pressure and the prevalence in type 1 diabetes patients ranges from 8-22% and in type 2 diabetes patients ranges from 5-48%.[5] At this stage patients will also experience gradual loss of renal function.
End-stage renal disease	Patients with untreated clinical diabetic nephropathy will subsequently develop end stage renal failure, needing treatment by dialysis to avoid death or uraemia. Patients with end-stage renal disease have a complete loss of renal function, hypertension and the prevalence in type 1 diabetes ranges from 2-5%. [5]

2.2.1 Prevalence of Diabetic Kidney Disease

The prevalence of microalbuminuria in type 1 diabetes was first described cross-sectionally in the early 1990's. Klein et al reported the prevalence of microalbuminuria to be 21% and proteinuria to be 21% in the Wisconsin Epidemiologic Study of Diabetic Retinopathy study cohort (Klein et al. 1992a). The prevalence of microalbuminuria in the Pittsburgh Epidemiology of Diabetes Complications Study was 22% and the prevalence of proteinuria was 27% (Orchard et al. 1990a). The incidence of nephropathy was first documented in type 1 diabetes (Boston) by Krolewski, which showed the cumulative incidence of nephropathy to be 35% in at 40 years disease duration (Mogensen 1984). Anderson et al also found the cumulative incidence of nephropathy in type 1 diabetes (Denmark) to be 41% at greater than 25 years of disease duration (Nelson et al. 1991).

2.2.2 Natural History of Diabetic Kidney Disease

The natural history of nephropathy has been well described, and is categorized according to urine albumin excretion rate (AER), as described in table 1. Microalbuminuria was shown to predict clinical proteinuria in diabetes in the early 1980's (Borch-Johnsen K & Deckert T 1992; Nelson et al. 1991). Additionally, an early population-based study of diabetes patients linked the albumin-creatinine ratio to overt nephropathy. This study, conducted by Nelson et al was one of the first to demonstrate and recommend that a single untimed urine specimen is an effective means of identifying subjects who are at risk for developing overt nephropathy (Nelson et al. 1991).

The degree of albuminuria has been detectable since the 1960's and predicts progression to more advanced renal disease and renal failure (Mogensen & Christensen 1984; Viberti G 1982). Three independent prospective studies have shown that AER predicts subsequent

nephropathy (Mathiesen et al. 1984; Mogensen & Christensen 1984; Parving et al. 1982; Steele 2001). The stages of nephropathy, outlined in Table 1, include microalbuminuria, clinical diabetic nephropathy, and then finally end stage renal disease.

2.2.3 Risk Factors for Diabetic Kidney Disease

There are several risk factors associated with nephropathy. Glycemic control is the major factor associated with disease risk. In type 1 and type 2 subjects, research from clinical trials has shown that achieving glycemic control near normal levels leads to a significant reduction in developing microalbuminuria and the risk of progressing from microalbuminuria to persistent proteinuria (Chase et al. 1991; Skyler 2001). Higher blood pressure and hypertension are associated with progression of diabetic renal disease (Krolewski et al. 1985). Epidemiologic studies have shown that the prevalence of hypertension is higher in patients with nephropathy than in patients with normoalbuminuria (Skyler 2001). Smoking also increases the risk of nephropathy progression (Andersen et al. 1983; Deckert et al. 1996). Male sex, disease duration and higher total cholesterol are also all independent risk factors for nephropathy and renal insufficiency (Klein et al. 1999; Sawicki et al. 1994).

2.2.4 Screening for Diabetic Kidney Disease

The ADA recommends yearly screening for nephropathy in type 2 patients and type 1 patients with 5 years of disease duration (American Diabetes Association 2005). Screening for nephropathy followed by appropriate treatment has been shown to be cost-effective for type 1 diabetes patients, using computer simulations (Palmer et al. 2000). The presence of nephropathy can be screened for and clinically assessed by urine collection and analysis for protein, which can occur in several ways (Skyler 2001). An albumin/creatinine ratio from a random spot urine collection can be performed. This is reasonable for initial screens, but positive results need to

followed by a 24-hour or timed urine collection. The sensitivity of spot urine testing ranges between 60%-89%, with a specificity of >80% (Schwab et al. 1992). There is also a 24 hour timed urine collection for albumunuria and creatinine or a timed (overnight or 3-4 hour) urine collection. Positive results need to be confirmed with a second measurement because of high variability in urine excretion in people with diabetes. There is marked day to day variability in albumin excretion, so at least 2 of 3 collections done in a 3 to 6 month period should show elevated levels before a patient is designated as having microalbuminuria (Skyler 2001). The gold standard for microalbuminuria assessment is the 24-hour albumin excretion rate, assessed by radioimmunoassay (American Diabetes Association 1999; Klein et al. 1992a; Webb et al. 1996). The sensitivity of the 24-hour AER test ranges from 60-97% and specificity of the test ranges from 77-97% (American Diabetes Association 1999; Coonrod et al. 1989; Hutchison et al. 1988; Kouri et al. 1991; Poulsen et al. 1992; Schwab et al. 1992; Shield et al. 1995; Webb et al. 1996). The 4-hour and overnight AER are extremely accurate and are often used as an 'alternative gold standard'. The correlation coefficients between 24 hour and 4-hour or overnight timed specimens are approximately .95 (Ellis et al. 1989; Tiu et al. 1993).

2.2.5 Prevention of Diabetic Kidney Disease

Nephropathy can be prevented and its progression slowed. Glyemic control and control of hypertension were found to inhibit the progression of nephropathy in the 1980's (Feldt-Rasmussen et al. 1986; Mogensen 1982). Strict glycemic control reduces risk of microalbuminuria and can reduce AER and prevent progression to overt proteinuria (Group 1993). Controlling blood pressure slows the rate of decline of renal function and improves survival (Group 1998; Maki et al. 1995). Pharmacologic therapies also exist to slow the progression of nephropathy. Angiotensin converting enzymes (ACE) inhibitors decrease

microalbuminuria and delay the progression of diabetic nephropathy following the onset of microalbuminuria, independent of hypertension status (Kshirsagar et al. 2000). ACE inhibitors reduce the rate of death, dialysis, or transplantation in type 1 diabetes patients with overt nephropathy and impaired renal function (Lewis et al. 1993). Clinical trials have shown that angiotensin receptor blockers (ARB) are effective antihypertensive agents and that they delay the progression of diabetic nephropathy to end-stage renal disease (Oparil et al. 2005; Rodby 2004). Dietary protein restrictions have also been shown to reduce rate of renal decline; the ADA recommends patients with clinic nephropathy limit protein to 10% of daily total calories (American Diabetes Association 2005). The treatments for nephropathy have been shown to be cost-effective given the tremendous costs associated with diabetic nephropathy and end-stage renal disease (Palmer et al. 2000; Rippin et al. 2004). Additionally, data from the Pittsburgh Epidemiology of Diabetes Complications suggest that proteinuria in diabeteic nephropathy may substantially regress in approximately 6% and improve in at least 34% of individuals with type 1 diabetes over a four-year period, often in association with a decrease in low density lipoprotein cholesterol concentration or stabilization or improvement in blood pressure (Ellis et al. 1996).

2.2.6 Treatment of Diabetic Kidney Disease

For patients with clinical nephropathy that progresses to end-stage renal disease, treatments for ESRD exist. Dialysis, in which an artificial kidney removes waste from the blood, is the most common treatment. There are two forms of dialysis, hemodialysis and peritoneal dialysis.[52] Both have side-effects that consist of high or low blood pressure, upset stomach, muscle cramps, nerve problems, anemia, bone disease, poor nutrition, and problems with infection. In addition, hemodialysis must be performed 2-3 days per week and takes 3-5 hours, and chronic ambulatory peritoneal dialysis takes 30-45 minutes and must be done 4-5 times a

day. Renal transplantation is the only treatment of ESRD that will eliminate renal dysfunction (American Diabetes Association 2004b).

2.2.7 Summary of Diabetic Kidney Disease

Persons with diabetes make up the largest group of end-stage renal disease patients. This disparity is due to diabetic nephropathy, which affects approximately 30% of all diabetes patients. The chances of developing diabetic nephropathy increase with hypertension, disease duration, smoking and hyperlipidemia. Screening urine for protein can detect early stages of nephropathy; as such the American Diabetes Association recommends annual screening for nephropathy. Coupled with early detection, strict glycemic control, blood pressure control, and use of medications such as ACE inhibitors can prevent or delay the progression of nephropathy.

2.3 Diabetic Eye Disease

2.3.1 Prevalence of Diabetic Eye Disease

Diabetic retinopathy is the leading cause of blindness among Americans between the ages of 20-74 (Aiello et al. 1998). Blindness is 25 times more common in people with diabetes than in people without diabetes (Klein et al. 1995b; Palmberg 1977). An estimated 63,000 cases of proliferative diabetic retinopathy (PDR), 29,000 high risk PDR cases, 80,000 macular edema cases, 56,000 clinically significant macular edema (CSME) cases and 5,000 new cases of legal blindness occur each year as a result of diabetic retinopathy (Klein et al. 1995b). There is a higher risk of more frequent and severe ocular complications in type 1 diabetes (Palmberg 1977). Approximately 25% of type 1 diabetes patients have retinopathy after 5 years, increasing to 60% and 80% after 10 and 15 years, respectively (Klein R et al. 1984). In type 2 diabetes, the presence of retinopathy also predicts mortality (Walters et al. 1994).

The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) was one of the first studies to document the prevalence and incidence of and risk factors for proliferative diabetic retinopathy. The WESDR was a longitudinal study using a population based cohort of diabetes patients from southern Wisconsin. The major finding of the study was that proliferative retinopathy is a prevalent complication in type 1 diabetes. The study found that at the 10 year follow-up point, 29.8% of the younger onset group, 23.6% of the older onset group taking insulin, and 9.7% of the older onset group not taking insulin developed retinopathy. Hyperglycemia, longer duration of diabetes, hypertension and more severe retinopathy at baseline were associated with risk of developing proliferative retinopathy (Klein et al. 1992b).

2.3.2 Natural History of Diabetic Eye Disease

Diabetic retinopathy is a general term for all disorders of the retina caused by diabetes. The major causes of visual loss from diabetic retinopathy are disturbances to the macula affecting central vision and profound retinal ischemia leading to proliferative retinopathy (C.J. & D.L. 1996). The stages of diabetic retinopathy are outlined in Table 2 (Aiello et al. 1998). There are two major types of retinopathy: proliferative and nonproliferative (American Diabetes Association 2004a).[10] Proliferative retinopathy is characterized by new blood vessels growing forward from the surface of the retina, referred to as neovascularization, in response to widespread retinal ischemia. New vessels are fragile and prone to bleeding causing sudden visual loss, which may be severe and prolonged. Continued proliferation may lead to permanent blindess (McCarty C 2001).

Nonproliferative retinopathy is characterized by vascular leakage within the retina. Macular edema is the most common cause of visual loss of nonproliferative retinopathy. It is characterized by the gradual accumulation of fluid and lipid in the macular region of the retina as a result of chronic retinal capillary leakage (McCarty C 2001). The incidence of proliferative retinopathy is greatest in people with type 1 diabetes, whereas the incidence of macular edema is highest in Type 2 diabetes (Begg I 2001).

Table 2

Stages of Diabetic Retinopathy

Stage	Characteristics
Early Stage	**Mild Non-proliferative diabetic retinopathy (NPDR)-**Increased retinal vascular permeability (can occur at this stage or any later stage, resulting in fluid accumulation in the retina); cotton wool spots
Middle Stages	**Moderate NPDR**-Intraretinal microvascular abnormality **Severe NPDR**-Retinal capillary loss **Very severe NPDR**-Retinal ischemia; extensive intraretinal hemorrhages and microaneurysms
Advances stages	**Proliferative diabetic retinopathy (PDR)-** Neovascularization in the retina and the new vessels are fragile and prone to bleed; This stage is also characterized by neovascularization of the iris, neovascular glaucoma, preretinal and vitreous hemorrhage, fibrovascular proliferation, retinal traction, retinal tears, retinal detachment

2.3.3 Risk Factors for Diabetic Eye Disease

There are many risk factors for diabetic retinopathy. Poor glycemic control is associated with retinopathy (Aiello et al. 1998). Elevated blood glucose is the strongest risk factor for predicting the incidence and progression of proliferative retinopathy, regardless of diabetes type (Klein et al. 1994). Both age and duration of diabetes are closely associated risk factors for retinopathy in people with type 1 diabetes (Aiello et al. 1998; Klein R 1988; Klein et al. 1984a; Klein et al. 1984c). Elevated blood pressure is a risk factor for proliferative retinopathy, macular edema, and loss of vision in both type 1 and type 2 diabetes (Klein et al. 1995a; Klein et al. 1995b; Klein et al. 1989; Moss et al. 1994a). Dyslipidemia has been associated with diabetic retinopathy. In the Early Treatment of Diabetic Retinopathy Study (ETDRS), the development and severity of retinal hard exudates in the macula were directly associated with elevations in the serum cholesterol and LDL cholesterol in type 1 and type 2 diabetes (Chew et al. 1996; Ferris et al. 1996; Klein et al. 1991). The presence of nephropathy is also a risk factor for retinopathy. Retinopathy and nephropathy are the most common microvascular complications of diabetes, have common risk factors and patients often have both (McCarty C 2001).

2.3.4. Screening for Diabetic Eye Disease

The American Diabetes Association recommends adults with type 1 diabetes have an initial dilated eye examination by an ophthalmologist or optometrist within 5 years after onset of diabetes and that type 2 diabetes patients should have an exam shortly after diagnosis (American Diabetes Association 2005). Subsequent examinations in type 1 and type 2 diabetic patients should be repeated annually by an ophthalmologist or optometrist who is knowledgeable and experienced in diagnosing the presence of diabetic retinopathy and is aware of its management. Less frequent eye exams may be considered with the advice of an eye care professional in the

setting of a normal eye exam (American Diabetes Association 2005). Retinopathy can be detected using several different methods of examination: direct opthalmoscopy, indirect opthalmoscopy, biomicroscopy with diagnostic contact lens, biomicroscopy with handheld lens, nonmydriatic camera photography, 7-standard field stereoscopic photography and digital camera photography. Stereoscopic photography was shown to be efficacious in detecting retinopathy in the landmark Early Treatment Diabetic Retinopathy Study (ETDRS) study (Group 1991). Direct opthalmoscopy by skilled examiner detects the presence of proliferative diabetic retinopathy with a sensitivity of 79% and specificity of 99% (Moss et al. 1985). The gold standard is the 7-field stereoscopic color fundus photography using a central reader (Moss et al. 1985).

2.3.5 Prevention of Diabetic Eye Disease

With appropriate screening and ophthalmologic care, >90% of visual loss resulting from diabetic retinopathy can be prevented (Ferris 1993). Timely evaluation and treatment are critical to prevent visual impairments (Aiello et al. 1998). Intensive glycemic control, vitrectomy, scatter photocoagulation and focal laser coagulation have been shown to prevent or delay progression of diabetic retinopathy. In the Diabetes Control and Complications Trial (DCCT) intensive glycemic control was shown to reduce the onset of retinopathy by 76% in patients with no diabetic retinopathy in type 1 diabetes. Among patients with nonproliferative retinopathy, the DCCT provided evidence that intensive glycemic control could reduce retinopathy progression by 63%, reduce development of nonproliferative and proliferative retinopathy by 47%, reduce the development of macular edema by 26%, and reduce the need for laser treatment by 51%.

2.3.6 Treatment of Diabetic Eye Disease

Data from clinical trials have shown the effectiveness of laser photocoagulation to treat retinopathy. The Diabetic Retinopathy Study (DRS) was one of the first landmark randomized

clinical control trials to find photocoagulation treatment for diabetic retinopathy to be efficacious. The DRS purpose was to evaluate photocoagulation for proliferative diabetic retinopathy. The study found that photocoagulation reduced severe vision loss by 50% or more (Diabetic Retinopathy Study Research Group 1981). The Early Treatment of Diabetic Retinopathy Study was one of the first studies to show that focal photocoagulation of clinically significant macular edema substantially reduces the risk of severe vision loss. In addition, focal treatment also increased the chance of visual improvement, decreased the frequency of persistent macular edema, and caused only minor visual field losses (Group 1985).

Among patients with clinically significant macular edema, focal laser photocoagulation results in a 50% reduction in moderate visual loss after 3 years. Scatter photocoagulation reduces severe visual loss after 3 years by 60% in patients with high risk proliferative retinopathy. Vitrectomy increases chance of 20/40 or better vision after 2 years by 60% in patients with severe proliferative retinopathy and severe vitreous hemorrhage (Aiello et al. 1998). Early detection of diabetic retinopathy has also been shown to be cost-effective, as treatment and detection of diabetic eye disease could potentially save $600 million dollars (Javitt 1995). Primary prevention programs aimed at improving eye care for patients with diabetes reduces needless vision loss and provides a financial return on the investment of public funds (Javitt et al. 1994).

2.3.7 Summary of Diabetic Eye Disease

Over three quarters of the diabetes population develops retinopathy over the course of their lifespan. Diabetic retinopathy is the most common cause of blindness in working age adults. Elevated glycemic levels, hyperlipidemia, and hypertension, are all associated with an increased risk of diabetic retinopathy. Dilated eye exams, performed by ophthalmologist or

optometrist detect early forms of retinopathy; as such the American Diabetes Association recommends annual retinal screenings. With screening and proper ophthalmologic care the majority of vision loss from diabetic retinopathy can be avoided.

2.4 Diabetic Foot Disease

Diabetic foot ulcers and lower extremity amputations are the major forms of diabetic foot disease. Half of all non-traumatic amputations occur in people with diabetes, although diagnosed diabetes patients make up only 6.3% of the population (Reiber 1995). Approximately 85% of all amputations are preceded by a non-healing foot ulcer and foot ulcers affect up to 15% of all people with diabetes (Palumbo 1985).

2.4.1 Peripheral Neuropathy

2.4.1.1 Prevalence of Peripheral Neuropathy

Peripheral neuropathy is associated with an 8-18 fold higher risk of ulceration and a 2-5 fold risk of amputation; because of different methods used to measure neuropathy, estimates vary and are difficult to assimilate (Dyck 2003; Lehto et al. 1996; Mayfield et al. 1996; McNeely et al. 1995; Reiber 1995; Selby & Zhang 1995; Young et al. 1994). One of the first studies to document the prevalence of peripheral neuropathy was the Rochester Diabetic Study, which was a longitudinal community based study of both type 1 and type 2 diabetes subjects, in which 54% of type 1 diabetes patients had peripheral neuropathy (Dyck et al. 1993). In another early study, the Pittsburgh EDC study found the prevalence of polyneuropathy in type 1 diabetes to be 34% and correlated with diabetic control, retinopathy, nephropathy, diabetes duration, and smoking(Maser et al. 1989b). Peripheral neuropathy occurs when patients have symptoms and or signs of peripheral nerve dysfunction in people with diabetes after exclusion of other causes (Neil et al. 1989).

2.4.1.2 Natural History of Peripheral Neuropathy

Peripheral neuropathy occurs in stages, as outlined in Table 3 (Mayfield et al. 1998). The increased risk for amputation and foot ulcers from peripheral nephropathy occurs through several

different mechanisms (Mayfield et al. 1998). There is a loss of protective sensations that include pain, pressure, and temperature, which removes the signals of damaging stimuli or conditions. The motor component of polyneuropathy results in atrophy of the intrinsic muscles resulting in a flexion deformity, which creates areas of increased pressure under the metatarsal heads and tips of toes (Mayfield et al. 1998). Identified risk factors for neuropathy among type 1 diabetes patients include glycemic control, disease duration, nephropathy and retinopathy (Maser et al. 1989b).

Table 3

Stages of Peripheral Neuropathy

Stage	Characteristics
Asymptomatic polyneuropathy	Phase 1- No symptoms or signs but neuropathic tests abnormalities (nerve conduction, quantitative sensory testing) Phase 2- Test abnormalities plus neuropathy impairment on neurological exam.
Symptomatic polyneuropathy	Phase 1- Symptoms, signs, and test abnormality; Clinical abnormalities include: chronic painful: burning, shooting, stabbing pains, reduced sensation to several modalities, reduced/absent reflexes; acute painful: severe chronic symptoms; painless with complete/partial sensory loss Phase 2- Phase 1 plus significant ankle dorsiflexor weakness
Disabling polyneuropathy	Late complications-Foot lesions, neuropathic deformity, nontraumatic amputation

2.4.1.3 Screening for Peripheral Neuropathy

Peripheral neuropathy is assessed clinically using various techniques. Patients may self-report symptoms or complete questionnaires constructed to assess signs objectively, such as the Neuropathic Disability Score or Neuropathic Impairment Score (Dyck 2003; Dyck et al. 1997). There are also simple devices available for clinical evaluation. The Semmes-Weinstein monofilament assesses pressure perception when gentle pressure is applied to the soles of the feet(Mayfield & Sugarman 2000; Valk et al. 1997). Sensitivities vary from 86-100% (Armstrong et al. 1998; Kumar et al. 1991; Miranda-Palma B et al. 2003). Inter and intra rater agreement kappa values are .72 and .83, respectively (Maser et al. 1989a). Sensitivity also has been reported to be .84-1.00 and specificity to be .77-1.00 (Kumar et al. 1991; Sosenko et al. 1990). The Rydel-Seiffer tuning fork tests for foot ulcers by using visual optical illusion to allow the assessor to determine the threshold in which foot sensation disappears (Shin et al. 2000; Thivolet et al. 1990). The tuning fork had a coefficient of variation of 6-8% in the same day by different examiners and 24% over several weeks by same examiner (Hilz et al. 1998; Liniger et al. 1990). A high degree of correlation was also found between experienced and inexperienced Rydel-Seiffer measurements($r=.87$, $p<.001$) (Hilz et al. 1998). Electrophysiological tests which measure nerve conduction by applying an electrical shock to the nerve are also performed (Criqui 2001). The Michigan Neuropathy Screening Instrument (MNSI) has been shown to be a reliable tool to comprehensively assess neuropathy (Bax et al. 1996; Feldman et al. 1994; Kastenbauer et al. 2004). The MNSI includes a clinical foot inspection, a test of ankle reflexes and of vibration perception, and a questionnaire concerning symptoms.

A consensus statement from the American Diabetes Association and American Academy of Neurology was developed in 1992 outlining standardized measurement in diabetic neuropathy (Diabetic Neuropathy Conference Proceedings 1992). This report stated that clinical measures for neuropathy should be taken for all patients, which includes medical and neurological history (directed score histories) and physical examination. Electrodiagnostic measures, such as nerve conduction studies, are sensitive, specific, and reproducible measures of the presence and severity of peripheral nerve involvement in diabetes patients. Quantitative sensory testing is the determination of the absolute sensory threshold, defined as the minimal energy reliably detected for a particular modality. It is relatively simple and noninvasive, and is a logical extension of the sensory portion of the clinical exam. Nerve biopsy is generally not recommended for routine for screening, because there is no direct benefit for the patient and is associated with morbidity (Diabetic Neuropathy Conference Proceedings 1992).

Since then, there have been advancements in the development and validation of specific tests that can be used for clinical exam and quantitative sensory testing. The clinical neurological exam and Semmes Weinstein Monofilament are rapid screening tests that predict which patients might develop foot ulceration with a high degree of sensitivity (Valk et al. 1997). Nerve conduction studies are strongly correlated with underlying structural changes and are the least subjective and most reliable single criterion standard, and considered the gold standard (Behse & Buchthal 1978; Bril 1994; Perkins et al. 2001).

2.4.2 Peripheral Vascular Disease

2.4.2.1 Prevalence of Peripheral Vascular Disease

Peripheral vascular disease, also referred to as lower extremity arterial disease (LEAD), is a condition characterized by atherosclerosis of the peripheral blood vessels (Kannel & McGee

1979). Peripheral vascular disease affects 12 million Americans (American Diabetes Association 2004c). Peripheral vascular disease is observed in 15% of patients at 10 years and 45% of people at 20 years of diabetes disease duration (Murabito et al. 1997). Peripheral vascular disease was initially documented in a cohort of diabetes patients from Rochester Minnesota, diagnosed with diabetes between 1945-1969. This study reported an 8% prevalence of PVD within this population in 1980. The cumulative incidence rose with age and duration of diabetes to reach 45% by 20 years of duration of diabetes (Melton et al. 1980).

Peripheral vascular disease is a major risk factor for amputation, and is associated with myocardial infarction and stroke (Weitz et al. 1996). Peripheral vascular disease plays a major role in delayed wound healing, gangrene, and is a contributing factor to almost half of the amputations (S.D. et al. 1993). Peripheral vascular disease reduces quality of life by contributes to long-term disability and functional impairment that is often severe (American Diabetes Association 2004c).

2.4.2.2 Natural History of Peripheral Vascular Disease

Peripheral vascular disease is characterized primarily by claudication and rest pain. Claudication occurs when there is pain in the calf that develops upon walking and is relieved within 10 minutes of rest (Pecoraro et al. 1990). Rest pain is more severe and is defined as pain that occurs at rest and is relieved by positioning of the legs (Mayfield et al. 1998). Other symptoms which are very severe, include tissue loss, gangrene, and critical limb ischemia (Mayfield et al. 1998). It is reported that ½ of peripheral vascular disease patients are asymptomatic or have atypical symptoms, 1/3 have claudication, and the remainder have more severe forms of disease (Hiatt 2001). Risk factors for peripheral vascular disease include age, disease duration, and cigarette smoking (American Diabetes Association 2004c; Bernstein &

Fronek 1982). Hypertension and hyperlipidemia are major risk factors for peripheral vascular disease (Stokes et al. 1987). Hypertension is associated with the development of atherosclerosis and a 2-3 fold increase in claudication in type 2 diabetes(Lee J. S. et al. 1993). In the Pittsburgh Epidemiology of Diabetes Complication Study cohort, longer disease duration, higher HDL and total cholesterol, hypertension, HbA1c level, higher LDL cholesterol and smoking were all positively correlated with peripheral vascular disease in type 1 diabetes (Forrest et al. 2000).

2.4.2.3 Screening for Peripheral Vascular Disease

Peripheral vascular disease is assessed clinically by visual inspection of the foot and palpation of peripheral pulses (American Diabetes Association 2004c). Identifying subclinical disease may prevent functional disability and limb loss. The recommended and most accurate test is the Ankle-Brachial Index (ABI). One of the first studies to discuss the usefulness of the ABI was conducted by McMillan and colleagues. This study showed an association between high ABI's and medial wall calcification (McMillan 1991). In subjects from the Rochester Minnesota cohort, the progression of peripheral vascular disese was associated with decreased post exercise ankle-brachial index (ABI), the presence of LEAD and diabetes at baseline, increased systolic blood pressure, and smoking (Melton et al. 1980; Orchard & Strandness 1993). The ABI is used to measure and quantify obstruction in arteries. The ABI measures the systolic blood pressures in the ankles and the arms using a hand held Doppler and then a ratio of the 2 measurements is calculated (American Diabetes Association 2004c). ABI detects subclinical disease. It has been validated against angiographically confirmed disease and found to be 95% sensitive and 100% specific (Bernstein & Fronek 1982).

2.4.3 Other Risk Factors for Diabetic Foot Disease

Demographic Factors have been linked to foot ulcers and amputation. Age and disease duration are associated with foot disease. The risk of ulcers and amputation increases 2 to 4 fold with both age and disease duration (Moss et al. 1992; Reiber 1995; Young et al. 1994). Gender has also been shown to be a risk factor for foot disease. In type 2 diabetes, male sex has been associated with a 1.6 increased risk of ulcers and with a 2.8 to 6.5 fold higher risk of amputation (Dyck 2003; Mayfield et al. 1996; Moss et al. 1992; Reiber 1995; Selby & Zhang 1995). Race has been associated with increased risk of amputation in a few studies. Hispanics and Blacks were shown to have a 2-fold risk and Pima Indians were shown to have up to four fold risk, compared to whites (Dyck 2003; Lavery et al. 1996; Reiber 1995).

Along with demographic factors, behavioral factors are associated with foot disease. Lack of social connectedness defined as living alone, no visits from friends or relatives in the past month, no attendance at social or religious gatherings, and personal dissatisfaction, is associated with a 2.1-3.8 fold higher risk of amputation (Reiber et al. 1992) Lack of patient education and self-care have been shown to be associated with over a three-fold increased risk of amputation (Reiber et al. 1992).

In addition to demographic and behavioral factors, health status factors such as glycemic control and co-morbid conditions as well as foot pathology, are associated with risk of diabetic foot disease. Poor glycemic control, hypertension, and hyperlipidemia increase risk for neuropathy and amputation (Dyck 2003; Lee J. S. et al. 1993; Lehto et al. 1996; Mayfield et al. 1996; Selby & Zhang 1995). Risk of foot disease is also associated with diabetic complications in other organ systems (Borssen et al. 1990; Dyck 2003; Mayfield et al. 1996; Rosenqvist 1984;

Selby & Zhang 1995). Altered foot biomechanics, such as increased plantar pressure, bony abnormalities, limited joint mobility, skin pathology are associated with risk of foot disease (Birke & Sims 1986; Ctercteko et al. 1981; Fernando et al. 1991; Mueller et al. 1989; Rosenbloom et al. 1982; Veves et al. 1992). History of prior foot ulcer is associated with 2 to 10.5 fold higher risk of amputation (Lee J. S. et al. 1993; Mayfield et al. 1996; Moss et al. 1992; Reiber et al. 1992).

2.4.4 Screening for Diabetic Foot Disease

The American Diabetes Association recommends a comprehensive foot exam annually on patients with diabetes to identify risk factors predictive of ulcers and amputations. Comprehensive examination of the foot includes assessment of neurological, vascular and biomechanical status (Mayfield et al. 1998). The American Diabetes Association also recommends a visual inspection of patient's feet at each routine visit. Visual inspection consists of a scan of the skin surface for breaks in the cutaneous barrier, increased warmth, and callus formation (Mayfield et al. 1998). High risk patients should be referred to foot care specialists for ongoing preventive care and lifelong surveillance (American Diabetes Association 2005). Proper foot wear is an important part of foot care. When fitted properly, foot wear can reduce abnormal pressures, reduce the formation of calluses and ulcers, and protect the foot from external trauma (Mayfield et al. 1998).

2.4.5 Prevention of Diabetic Foot Disease

Foot care programs can decrease the rate of ulcers and amputations by 44 to 85% (Assal et al. 1985; Davidson et al. 1981; Edmonds M.E. et al. 1988; Litzelman et al. 1993; Runyan et al. 1980). Prevention programs usually include a thorough foot risk assessment, callus and nail care, customized wound care, and patient education provided by a multidisciplinary team with

special expertise in the foot (Mayfield et al. 1998). Preventing peripheral neuropathy and peripheral vascular disease reduces risk of foot disease. The main peripheral neuropathy preventive strategy is glycemic control. In the DCCT, glycemic control resulted in a 69% reduction in subclinical neuropathy and a 57% reduction in clinical neuropathy in type 1 diabetes (Group 1993). The main primary preventive strategy for peripheral vascular disease in control of hypertension (Mayfield et al. 1998). For peripheral vascular disease secondary prevention, the goal is to improve functional capacity. For intermittent claudication exercise rehabilitation is recommended (Creasy et al. 1990; Larsen & Lassen 1966; Leng G.C. 2000; Williams et al. 1991). Angioplasty and vascular bypass surgery are treatment options as well, and have been used in the management of peripheral vascular disease since the 1970's (Currie et al. 1995; Tunis et al. 1991). Pharmacologic therapies to treat peripheral vascular disease, such as pentoxifylline and cilostazol, are also available (Dawson et al. 2000; Regensteiner et al. 2002).

2.4.6 Summary of Diabetic Foot Disease

Diabetic foot disease is comprised of foot ulcers and lower-extremity amputation. Diabetes patients make up the largest portion of individuals with non-traumatic amputations. Demographic, behavioral, and health status factors have all been associated with foot disease, but the presence of peripheral neuropathy and peripheral vascular disease convey the greatest risk of developing diabetic foot disease. Diabetes foot care programs that include screening for peripheral vascular disease and peripheral neuropathy can prevent foot disease by up to 85%.

2.5 Coronary Heart Disease

2.5.1 Prevalence of Coronary Heart Disease

Coronary heart disease is a significant cause of illness, disability and death among individuals with diabetes. Coronary heart disease, a form of cardiovascular disease (CVD), occurs when the arteries that supply blood to the heart muscle become hardened and narrow due to atherosclerosis (U.S. Department of Health and Human Services 2006). Macrovascular complications of diabetes, which include coronary heart disease, cerebrovascular disease, and peripheral vascular disease, account for more than 70% of all deaths in individuals with diabetes (American Diabetes Association 2002a; U.S. Department of Health and Human Services 2006). Coronary heart disease events are more common, occur at a younger age, and have a much greater case fatality rate in individuals with diabetes (Miettinen et al. 1998). People with diabetes who have no history of vascular disease have the same risk of having a heart attack or dying from vascular disease as nondiabetic individuals with a prior history of vascular disease (Haffner et al. 1998; Mukamal et al. 2001).

2.5.2 Natural History of Coronary Heart Disease

The pathogenesis of diabetic CVD and coronary heart disease is not fully understood, but it is likely that it is directly influenced by the diabetic state because atherosclerotic lesions occur earlier in age and with greater severity in people with diabetes (Vinik & Flemmer 2002). Atherosclerosis is influenced by abnormalities of the blood vessel wall, a hypercoaguable state, and alterations in blood flow (Vinik & Flemmer 2002).

The United Kingdom Prospective Diabetes Study (UKPDS) was one of the first major prospective studies to describe the prevalence and risk factors for cardiovascular disease and coronary heart disease in diabetes patients (Turner 1998). The objective of the UKPDS was to

determine whether glycemic control in type 2 diabetes would prevent diabetes complications. This study was initiated in 1977, and enrolled 5,102 people with newly diagnosed diabetes. At baseline 8% of the cohort had coronary heart disease and 39% had hypertension. After 9 years of follow-up, 20% had some form of coronary heart disease or stroke, and one third of these subjects died (Turner 1998). Among patients with no coronary heart disease at baseline, risk factors for developing coronary heart disease were low HDL concentration, elevated LDL concentrations, elevated HbA1c, elevated blood pressure, cigarette smoking, age, and male sex, with elevated LDL cholesterol and blood pressure being the strongest predictors (Turner et al. 1998).

2.5.3 Risk Factors for Coronary Heart Disease

The major risk factors for coronary heart disease are elevated cholesterol and blood pressure levels. The Centers for Disease Control reports that 70-97% of individuals with diabetes have dyslipidemia (Fagot-Campagna A et al. 2000). Elevated low-density lipoprotein cholesterol is a risk factor for cardiovascular disease. In the United Kingdom Prospective Diabetes Study (UKPDS), the risk of either angina or myocardial infarction increased 1.57 fold for every 1mmol/L increase in LDL cholesterol (Turner et al. 1998). Serum cholesterol was shown to be related to prevalence of coronary heart disease in the Steno clinic type 1 diabetes population (Jensen et al. 1987). Elevated blood pressure is also a major risk factor for coronary heart events, such as myocardial infarction (MI) and stroke, as well as microvascular complications in type 1 and type 2 diabetes (Arauz-Pacheco et al. 2002; Senior et al. 2005). Hypertension affects 20-60% of people with type 1 and type 2 diabetes (Arauz-Pacheco et al. 2002; Maahs et al. 2005). The prevalence of hypertension in diabetic populations is 1.5-3 times higher than in non-diabetic age matched groups (D.L & E 1995). In the UKPDS study, men with

hypertension were more likely to develop coronary heart disease and have non-fatal and fatal myocardial infarction (Turner et al. 1998). Additionally, in the UKPDS blood pressure lowering trial, tight blood pressure control achieved a clinically significant reduction in deaths related to diabetes, complications related to diabetes and progression of diabetic retinopathy (Group 1998). In the Pittsburgh Epidemiology of Diabetes Complications study, the prevalence of coronary heart disease was associated with longer disease duration, hypertension, nephropathy, and higher triglyceride levels (Maser et al. 1991).

There are several other risk factors for coronary heart disease. Glycemic control is a risk factor for cardiovascular events in people with type 1 and type 2 diabetes (Andersson & Svardsudd 1995; Fu et al. 1993; Gall et al. 1995; Gerstein H.C. et al. 2001; Lehto et al. 1999; Moss et al. 1994b; Wei et al. 1998). Among type 1 diabetes patients, the WESDR study found HbA1c was significantly related to the 4-year incidence of ischemic heart disease (Klein 1995). The presence of microvascular complications is also a risk factor for coronary heart disease. Microalbuminuria doubles the risk of coronary heart events in people with diabetes (Dinneen & Gerstein 1997; Gall et al. 1995). Clinical proteinuria consistent with diabetic nephropathy increases the risk of coronary events and total mortality greater than 2-fold (Agewall et al. 1997). Proliferative retinopathy, macular edema, visual impairment, and cataracts are risk factors for ischemic heart disease mortality in people with type 1 and type 2 diabetes (American Diabetes Association 2005). Epidemiologic analysis has shown proliferative retinopathy to be associated with an 11-fold increase risk of ischemic heart disease and macular edema a 2-fold increased risk of ischemic heart disease (American Diabetes Association 2005). The presence of metabolic syndrome has also between shown to predict coronary heart disease (Wannamethee et al. 2005).

Additionally, cardiac autonomic neuropathy has been linked to coronary heart disease in diabetes patients (Nesto 2004; Resnick & Howard 2002).

2.5.4 Screening for Coronary Heart Disease

The American Diabetes Association recommends annual screening for cardiovascular disease and coronary heart disease risk factors, consisting of blood pressure readings and lipid panels. All patients with diabetes should have blood pressure measured at the time of diagnosis and at each scheduled diabetes visit (American Diabetes Association 2005). The goal for hypertension control for diabetes patients is 130/80 mm Hg. The blood pressure measurement should be performed in the supine and standing position. Two or more determinations in each position should be obtained using an appropriately sized cuff. Hypertension should be diagnosed when blood pressure levels exceed 130/80 mmHg on at least two separate occasions, separated by at least one week (Arauz-Pacheco et al. 2002). In adults, lipid disorders should be tested for at least annually, and more often if needed to achieve goals (American Diabetes Association 2005). In adults with low-risk lipid values, defined as having a LDL<100mg/dl, or HDL >50 mg/dl, or triglyceride level <150 mg/dl, lipid assessments should be performed at least every 2 years (American Diabetes Association 2002b; Bagdade et al. 1967; U.S. Department of Health and Human Services 2006).

2.5.5 Prevention of Coronary Heart Disease

To prevent macrovascular complications in patients with diabetes, equal effort must be applied to controlling lipid levels and blood pressure (American Diabetes Association 2002b). Intensive glycemic control therapy may decrease elevated total and LDL cholesterol and in some cases be associated with rises in HDL cholesterol (Bierman 1992; Pietri et al. 1980). In the UKPDS, each 10 mmHg decrease in mean systolic blood pressure was associated with a

reduction in the risk of 12% for any complication related to diabetes, 15% for deaths related to diabetes, 11% for MI, and 13% for microvascular complications (Curb et al. 1996). Primary prevention efforts also must include alcohol intake moderation, smoking cessation, physical activity, and diet. The American Diabetes Association recommends diabetes patients participate in 30-34 minutes of moderate physical activity 3-5 days per week when possible. The ADA also recommends weight loss for all overweight and obese diabetes patients (BMI>25), and a moderate reduction in caloric intake for such individuals (500-1,000 kcal per day reduction) (American Diabetes Association 2005).

2.5.6 Treatment of Coronary Heart Disease

Therapies aimed at reducing blood pressure and lipid levels are effective in diminishing risk of coronary heart disease and cardiovascular events. In people with diabetes, interventions with diuretics, beta-blockers, calcium-channel blockers, and ACE inhibitors that decrease systolic blood pressure by 5 to 10 mmHg result in a 20-30% risk reduction in cardiovascular events (Curb et al. 1996; Cutler et al. 1997; Estacio et al. 2000; Hansson et al. 1998; Shepherd et al. 1995; Tuomilehto et al. 1999). Sodium restriction has not been tested in the diabetic population, however it has been shown in clinical trials that sodium restriction reduces blood pressure (Downs et al. 1998). Moderate physical activity, smoking cessation, and moderation of alcohol intake are also recommended to reduce blood pressure (American Diabetes Association 2005). Using computer simulated models, reductions in blood pressure and lipid levels have been associated with decreases in the total monetary costs of complications (Pyorala et al. 1997). Pharmacologic therapies, such as statins, ACE inhibitors, aspirin, and beta blockers, are also available to reduce cardiovascular and coronary heart disease events. In type 2 diabetes subjects, statins have been shown to lower lipid levels and reduce risk of coronary heart disease between

19-55% (Goldberg et al. 1998; LIPID Study Group 1998; Sacks et al. 1996). The addition of ACE inhibitors to other effective therapies reduces the risk of coronary heart events by 25% in high risk people with diabetes (Tuomilehto et al. 1999). A few trials show aspirin therapy reduces the risk of coronary heart events in high risk people with diabetes mellitus (Hoogwerf et al. 1999). Subgroup analyses involving diabetes patients show consistent mortality reduction due to beta-blockers in diabetic patients with established coronary artery disease (Gundersen & Kjekshus 1983; Helgeland et al. 1984; ISIS Study Group 1986; Jonas et al. 1996; Kjekshus et al. 1990; Malmberg et al. 1989; William-Olsson et al. 1979).

2.5.7 Summary of Coronary Heart Disease

Coronary heart disease is a major contributor to morbidity and mortality in diabetes. The most significant risk factors for cardiovascular disease are hyperlipidemia and hypertension, which data have shown are very prevalent in the diabetes population. The American Diabetes Association recommends annual screening for cardiovascular disease that includes blood pressure and lipid panel testing. Coronary heart disease can be prevented or its affects ameliorated largely by controlling blood pressure and lipid levels.

3.0 Screening literature

Screening for subclinical disease is a standard and important part of public health practice because of its potential for preventing the onset of severe disease. However, for screening to be of true utility, certain criteria must be met. First, the disorder for which screening is to be conducted should be well defined, i.e. the natural history and the nature of the disorder should be well understood and its clinical features easily identifiable. Additionally, the prevalence and rate of progression of the disorder should be well known. The disorder should by asymptomatic in its early stages, but if left untreated lead to significant morbidity. For a screening technique to be beneficial, an effective treatment for the condition should be available. Finally, the screening method should be simple and safe, discriminate between affected and unaffected individuals, and be cost-effective (KC 1994).

Screening tests to assess early stages of chronic diabetes-related complications and risk factors for these complications have met the aforementioned criteria. The features of each complication and associated screening test were described in previous chapters. The natural history and characteristics of each complication has been defined, and the prevalence has been documented. Each of these disorders has a treatable asymptomatic phase and a potential to advance to a severe late-stage form of the disease if left untreated. The effectiveness of the screening tests for the different chronic diabetes-related complications has been described according to how it functions, sensitivity and specificity, and cost-effectiveness.

The American Diabetes Association has set standards of care for diabetes patients based upon evidence from scientific research and expert opinion (American Diabetes Association 2005). The data have shown that early detection and therapy may prevent or delay many chronic diabetes complications. Current recommendations include an annual dilated eye exam to screen

for retinopathy, an annual foot exam to screen for foot disease and risk factors for foot disease and annual microalbuminuria testing to screen for nephropathy(American Diabetes Association 2005). The ADA also recommends screening for cardiovascular disease risk factors, which include an annual lipid panel and blood pressure reading at each physician visit. Additionally, as glycemic control is linked to the development of many chronic complications, quarterly HbA1c testing is recommended as well (American Diabetes Association 2005).

Screening practices in people with diabetes have been examined in several reports. These studies are often characterized by different study populations, different definitions of screening, differing criteria for satisfying screening recommendation and different correlates of screening. Screening data have been collected from health maintenance organizations, population based data, and national representative samples. A review of selected literature describing screening prevalence literature is provided in Appendix Table A1. Reported rates for cholesterol screening ranged from 42%-85.3%, rates for eye exams ranged from 18.9%-77.9%, rates for foot exams ranged from 27.2%-68.2%, rates for urine protein screen ranged from 17%-77%, and rates for HbA1c test ranged from 16.3%-89.0% (Ahluwalia et al. 2000; Beckles et al. 1998; Centers for Disease Control and Prevention 2002a; Centers for Disease Control and Prevention 2002b; Clark et al. 2001; Engelgau et al. 1998; Kerr et al. 2004; Laditka et al. 2001; Martin et al. 1995; Miller et al. 2000; Ozminkowski R et al. 2000; Peters et al. 1996; Petitti et al. 2000; Saaddine et al. 2002; Schoenfeld et al. 2001; Sikka et al. 1999; Simon et al. 1999; Streja & Rabkin 1999; Weiner et al. 1995). Correlates of receipt of screening tests identified in the literature include having health insurance, higher education level, female gender, and older age. Detailed information regarding screening correlates identified from selected literature is included in Appendix Table A2 (Ahluwalia et al. 2000; Beckles et al. 1998; Centers for Disease Control and

Prevention 2002a; Centers for Disease Control and Prevention 2002b; Clark et al. 2001; Engelgau et al. 1998; Laditka et al. 2001; Martin et al. 1995; Miller et al. 2000; Ozminkowski R et al. 2000; Peters et al. 1996; Petitti et al. 2000; Saaddine et al. 2002; Schoenfeld et al. 2001; Sikka et al. 1999; Simon et al. 1999; Streja & Rabkin 1999; Weiner et al. 1995).

The prevalence of screening for chronic complications and risk factors for complications has been investigated using data from several health maintenance organizations. Analysis of the health maintenance organization CaliforniaCare data from 1997 revealed that 77.9% of their diabetes patients self-reported a retinal exam, 65.2% reported a foot exam, and 89.0% reported HbA1c testing in the previous year (Simon et al. 1999). Correlates of screening included older age, seeing a dietician, self-monitoring of blood glucose, and visits to a diabetes educator. Peters et al reviewed medical charts of patients enrolled in a large HMO in California for receipt of HbA1c tests, urine protein exams, foot examinations, and cholesterol screening according to ADA recommendations(Peters et al. 1996). This study found that 44% had one or more HbA1c test, 56% had a total cholesterol test, 48% had a urine protein test, and that documented foot exams occurred in 6% of office visits. Kaiser Permanente reported screening rates for HbA1c, lipid profiles, and microalbuminuria screenings between 1994-1997 for their diabetes patients (Petitti et al. 2000). In that population, 1997 screening rates were as follows: 64% had a HbA1c, 42% had a lipid profile, 33% were screened for microalbuminuria. Data from patients enrolled in 35 health plans across the United States compiled by the MEDSTAT group were analyzed to show rates of ophthalmology visits, HbA1c tests, and cholesterol tests for the year 1996. These data showed only 29% had an ophthalmology visit documented, 20% had at least 2 HbA1c tests documented, and 43% had at least one total cholesterol test documented (Ozminkowski R et al. 2000).

Data on screening patterns has also been investigated using data collected from national databases. Beckles et al analyzed 1994 Behavioral Risk factor Surveillance System (BRFSS) data and looked at foot exams, dilated eye exams, HbA1c, self-monitoring of blood glucose, and visits to health care provider (Beckles et al. 1998). In this report, type 1 diabetes was defined as currently using insulin and less than 30 years of age at disease diagnosis, and type 2 diabetes was defined as currently not using insulin or disease diagnosis at 30 years of age or greater. The results showed that overall, 61% reported a foot examination and 61% reported a dilated eye exam in the previous year. Type 1 diabetes patients made up 8.5% of the population, and among them 78.8% reported at least 1 HbA1c test, 63.6 reported a foot exam, and 74.9% reported having a dilated eye exam in the past 12 months. The presence of health insurance coverage and at least high school education were found to be positively correlated with screening. This study found that only 1% of non-insulin users and 3% of insulin users met all recommended screening criteria for the study.

Analysis of the Third National Health and Nutrition Survey and the 1995 BRFSS revealed that 85.3% of the diabetes respondents had cholesterol monitored biannually, 63.3% had an annual dilated eye exam, 54.8% had an annual foot exam, and 28.8% had at least one HbA1c test done in the previous 12 months (Saaddine et al. 2002). Correlates of screening were the presence of health insurance coverage, older age, and insulin use. Data from the 2002 BRFSS data indicated 69.7% of diabetes patients reported receiving a dilated eye exam, 68.2% reported receiving a foot exam, and 71.2% reported having at least 2 HbA1c tests (Centers for Disease Control and Prevention 2002b).

Research documenting screening behavior has primarily come from data collected though national surveys or administrative files from insurance groups. While both types of studies have

provided important information regarding screening, each is associated with several limitations. The national surveys used to report screening prevalence are the Behavioral Risk Factor Surveillance System (BRFSS) and the Third National Health Nutrition Examination Survey (NHANES III). The BRFSS is a telephone survey that is conducted continuously throughout all 12 months of the year. The study sample includes only non-institutionalized individuals with a residential phone. All data collected by the BRFSS is self-reported and are subject to recall bias. The BRFSS contains a diabetes module with questions specific to diabetes, but not all states use the module. Additionally, the screening questions asked by the BRFSS are very general, and only refer to dilated eye exams and foot exams. The screening questions do not ask who specifically is performing the eye exam or how comprehensive the foot examination is. Data on risk factors for cardiovascular disease are collected as a part of another module and are optional, and these data are often not reported alongside diabetes-specific information. Additionally, no data regarding screening for nephropathy are collected from diabetes patients. The NHANES III was conducted between 1988-1994, and consists of a home interview and clinical exam. Only non-institutionalized adults were included. NHANES III reported data are not related directly to screening, but rather to clinical exam data such as lipid, HbA1c, and blood pressure levels. When analyzing data from these surveys, it is important to note that these are not meant to be diabetes-specific surveys, but rather the intent is to collect data on a wide-range of health conditions that can be compared between states and survey points and can be used to determine policy. As such, the scope of diabetes questions is very limited and by no means a comprehensive way to look at preventive care among diabetes patients. For instance, there is very limited information regarding glycemic control and health care utilization related to

diabetes care collected. These factors may be associated with screening, but it is not possible to fully explore this with these data sets.

The second main source of screening data in the literature comes from insurance groups. Patient data collected from administrative databases are used to report screening information. The major limitation here is that these data may not represent screening in the general population, as the individuals in these groups had access through insurance coverage. Additionally, many of these insurance groups were based in California, which may not represent the general United States population. Use of administrative data is also associated with the potential for coding errors, which may underestimate or overestimate true screening prevalence.

The present screening literature, regardless of data source, has several limitations. There are very little data available on the factors that may predispose or prevent an individual to get screened. Most information reported in the literature addresses only screening prevalence. However, in order to begin to design interventions to improve screening rates, more data on the correlates of screening are needed. An additional observation from the literature is that the overwhelming majority of the diabetes subjects described in published reports are type 2 diabetes patients, which limits the generalizability to type 1 diabetes subjects. Also, the classification of type 1 diabetes status is crudely done, and often based upon insulin status and age at diagnosis. It is possible for misclassification of diabetes type, as some persons with type 2 diabetes were diagnosed before the age of thirty, and the age of starting insulin use is not asked. Type 1 diabetes patients are a unique diabetes sub-population, as these individuals are young and within the productive phase of their lives, and research suggests they may have more severe disease than type 2 diabetes patients (Laditka et al. 2001).

Also, not all studies used ADA screening criteria when evaluating screening rates and of those who did use ADA criteria, very few of these studies examined all ADA recommended screening tests. ADA screening guidelines are a part of recommended diabetes standards of care, and have been established to ensure the best level of care for diabetes patients, based upon expert opinion and clinical research. To truly examine the level of screening and overall care of diabetes patients, it is important to use these criteria. Likewise, it is important to look at all recommended screening tests for complications and risk factors for complications because all are necessary for optimal preventive care. The overwhelming majority of studies did not look at all screening tests, and the ones that did looked at them individually. In addition, an extremely small portion of the studies looked at combination of screening tests, and their definitions of complete screening varied. This limits comparability between the studies, but still none contained all ADA recommended tests.

4.0 Thesis contribution to the literature

Diabetes is a metabolic disorder affecting millions of Americans (Engelgau et al. 2004). Diabetes patients are at risk for developing complications, such as nephropathy, retinopathy, peripheral neuropathy, peripheral vascular disease, and cardiovascular disease (Engelgau et al. 2004). Diabetic nephropathy is the leading cause of end-stage renal disease, and approximately 30% of patients develop nephropathy. Almost all diabetes patients have some form of retinopathy, which is the leading cause of blindness among working age adults (Centers for Disease Control and Prevention 2005). Peripheral neuropathy and peripheral vascular disease, risk factors for foot disease, affect almost half of all diabetes patients (Centers for Disease Control and Prevention 2005). As a consequence of foot disease, the majority of lower extremity amputations occur in diabetes patients (Centers for Disease Control and Prevention 2005). Additionally, a major cause of mortality among diabetes patients is cardiovascular disease (Centers for Disease Control and Prevention 2005).

Chronic complications can be prevented or their progression delayed with early detection and treatment. Methods of early detection of subclinical disease or risk factors for disease as well as treatments to modify and ameliorate early stages of disease are available. The American Diabetes Association recommends routine screening for chronic complications and risk factors for complications (American Diabetes Association 2005). Despite evidence and clinical recommendations, few diabetes patients receive all recommended screening tests. One of the goals of Healthy People 2010 is to increase preventive care practices among persons with diabetes, which includes increasing the proportion of individuals having annual dilated eye exams, foot exams, and HbA1c tests (U.S. Department of Health and Human Services 2000).

The research conducted to date that has focused on screening for chronic diabetes complications has provided valuable information, but also has numerous limitations. Not all studies examined screening according to ADA recommended guidelines, and very few looked at all recommended screening tests. Additionally, the correlates of screening behavior examined in these studies have been very limited, primarily restricted to sociodemographic variables. These research studies consisted largely of type 2 diabetes populations, however examining screening behaviors in type 1 diabetes patients is important as data suggests these patients may be more at risk for developing complications (Laditka et al. 2001).

Although the current literature has supplied useful data to document the problem of screening in diabetes patients, there are still several areas that warrant further exploration, to portray the true picture of screening. There is still a need for research providing data related to recommended screening for all complications. All tests are needed for proper diabetes care and to ensure the most favorable disease outcomes. It is therefore of value to provide research related to complete screening. Likewise, more evidence is needed on how behavioral factors, health care access, and health status relate to screening. Previous research has largely been limited to sociodemographic variables, however these additional pieces of information are necessary to truly begin designing interventions and policies to address the screening problem. Finally, type 1 diabetes patients are not well-represented in the screening literature. Type 1 diabetes affects younger persons in the productive phase of their lives who research suggests may have a greater burden from complications than type 2 patients (Laditka et al. 2001). It is therefore of great utility to examine screening patterns in this sub-group of diabetes patients.

The research in this thesis will address several of the aforementioned limitations. This work will focus on confirmed type 1 diabetes patients. We will look at screening behaviors in

this unique group of diabetes patients, with the hopes of uncovering evidence that may be used to improve diabetes care in this population. This research will look at screening tests recommended for all chronic complications. Optimal disease management requires all of these tests be performed to ensure best disease outcomes, therefore it is important to conduct research in the same manner. Additionally, this work will also go beyond characterizing screening according to demographics and health status. It will look at the relationships between behavioral factors such as glycemic control, health care access, and clinical risk factors and screening. The findings from this study will provide evidence from which interventions and policies can be formed to facilitate screening for chronic diabetes-related complications and contribute to overall improvements in disease management

5.0 General Methodological Approach

Three manuscripts form the basis of this thesis. They explore the prevalence and predictors of screening in type 1 diabetes patients. Study subjects in these manuscripts will be drawn from a large cohort of persons with type 1 diabetes in Western Pennsylvania, enrolled in the Pittsburgh Epidemiology of Diabetes Complications Study cohort. The following section outlines and describes characteristics of this cohort and the broad aims of this investigation. Specific details about subjects from the study population used in this research will be provided in individual manuscripts.

5.1 The Pittsburgh Insulin-dependent Diabetes Mellitus (IDDM) Registry

All patients in the Pittsburgh Epidemiology of Diabetes Complications Study were identified from the Pittsburgh IDDM Registry. The Pittsburgh IDDM registry was designed to ascertain all new cases of IDDM under the age of 20 who were Allegheny County residents at the time of diagnosis and who were diagnosed after 1964 (LaPorte et al. 1981). The incidence of IDDM for the registry was obtained via review of hospital records and surveillance of pediatricians for the years 1965-1994. Monthly listings of hospital discharges from 25 general hospitals and one large children's hospital (Children's Hospital of Pittsburgh) in Allegheny county as compiled by the Hospital Utilization Project (HUP) were inspected and records were requested for all discharges where diabetes was the primary diagnosis and the patient was less than 20 years old. Hospital records at time of diagnosis were obtained for over 90% of cases. To check completeness of ascertainment, all pediatricians in Allegheny County were requested to identify children under their care who met all criteria for inclusion in the registry. There was a 92% response rate and this survey revealed that all children fulfilling the criteria were seen an area hospital. For each case, demographic information, date of diagnosis, referring and attending

physicians, history of onset of symptoms, and family history of diabetes data was obtained. The registry was updated every five years, with the last update in 1994. There were a total of 1,563 cases identified between 1965-1989 that comprised the registry, of which 53% were male and 90% were white (Dokheel 1993; Nishimura et al. 2001). The last published data described subjects added to the registry during the last updated period, January 1, 1990-December 31, 1994. During this time period, there were 257 type 1 diabetes patients added to the registry, of which 55% were male and 82% were white (Libman et al. 1998).

5.2 The Pittsburgh Epidemiology of Diabetes Complications Study

The Pittsburgh Epidemiology of Diabetes Complications study (EDC) cohort is comprised of subjects with childhood onset (<17 years) IDDM patients seen at or within one year of diagnosis at the Children's Hospital of Pittsburgh. Diabetes patients were eligible for the EDC study if they had previously participated in the Pittsburgh IDDM Mortality and Morbidity Follow-up Survey, conducted between 1981 and 1985, and lived within 100 miles of Pittsburgh (Orchard et al. 1990a; Orchard et al. 1990b).

Participation involved completing three self-report questionnaires that consisted of a 1)medical history and health behavior, which included the Rose questionnaire for angina and claudication; 2)physical activity questionnaire; and 3)various psychosocial questionnaires. Subjects were given a clinical exam to assess risk factors for and presence of cardiovascular disease, nephropathy, neuropathy, peripheral vascular disease, and retinopathy. All eligible participants were sent a letter inviting them to participate, and were subsequently contacted by telephone to schedule an appointment. If a participant refused or failed to keep appointments, they were asked to complete questionnaires and return them by mail. Two weeks before their scheduled appointments, participants were mailed the three questionnaires and containers (with

detailed instructions) to collect a 24-hour urine sample and a separate overnight urine sample which were kept frozen until the clinic appointment (Orchard et al. 1990a).

There were a total of 979 eligible patients, of which 788 (80%) participated at baseline. Among the 788 who participated, 657 (67%) gave full participation and 131 (13%) completed questionnaires only. More than 95% of the subjects were seen between May 1986 and September 1988. Among those with full participation, 51% were male, 13% had a disease duration of less than 10 years, 42% had a duration between 10-19 years, 34% had a duration between 20-29 years and 11% had a disease duration 30 years or greater the among those with full participation all at baseline (Orchard et al. 1990a).

5.3 Specific Aims

Large scale morbidity, mortality, disability and health expenditures are attributable to diabetes, thus making it a major public health issue. The majority of diabetes burden is due to associated chronic conditions that include retinopathy, nephropathy, neuropathy, peripheral vascular disease, and coronary heart disease. Presently, there are screening tests available and therapies to detect and treat early forms of these conditions, respectively. Routine screening for complications and their risk factors is recommended by the American Diabetes Association and considered a part of proper disease management. Despite the benefits of screening and the fact that it is a part of quality diabetes care, few diabetes patients receive screening at the recommended levels. To date, the literature which describes screening practices has largely focused on individuals with type 2 diabetes. However, persons with type 1 diabetes are a special group of diabetes patients, as they are diagnosed with disease at younger ages, while in the productive phase of their lives, and research suggests they may be more likely to develop complications than type 2 diabetes patients. Currently, there is a need for research that investigates the issue of screening as it applies to persons with type 1 diabetes.

The objective of this thesis is to examine screening for chronic diabetes complications among type 1 diabetes patients. The specific research aims of this thesis are:

1. Identify the frequency and trends in screening for chronic complications in a population of type 1 diabetes patients.

To date, the majority of studies have addressed screening practices among type 2 diabetes patients. Little is known about the prevalence of screening practices among persons with type 1 diabetes. It is important to identify screening trends and determine if this group of patients has been benefiting from evidence-based guidelines regarding screening and secondary prevention.

The purpose of this aim is to describe the prevalence of screening among type 1 diabetes patients, and to describe screening trends over time in this population.

We propose that:

a) The frequency of screening rates for chronic diabetes complications in this cohort of type 1 diabetes patients will be higher than screening levels reported in the published literature that largely described type 2 diabetes patients.

b) Screening rates will occur at lower rates than recommended by the American Diabetes Association.

c) Screening rates are improving over time in this cohort of type 1 diabetes subjects.

2. Identify general correlates of screening in a population of type 1 diabetes patients.

The purpose of this aim is to identify which factors that influence screening behavior in the type 1 diabetes population.

A) We propose that correlates of screening in this cohort will differ from those found in the general type 2 diabetes population.

Several studies indicate that the health system and health status of an individual are two important indicators for use of chronic disease screening tests in the general population. The influence of these issues on screening for chronic diabetes complications in the type 1 diabetes population, however, is unknown. Thus, this dissertation also examines these issues in the following manner.

2a. To evaluate the influence of patient behavior and health care access factors on receipt of screening tests.

Appropriate diabetes management is jointly dependent upon efforts from patients, providers, and the health care system. Randomized controlled trials have consistently shown that

improvements in diabetes processes of care such as screening as well as areas of disease management can be achieved by interventions that incorporate all of these components. However it is often difficult to translate multi-dimensional interventions into practice, and they are rarely able to be adopted in full. It is therefore important to determine which disease management factors have the greatest influence on screening, and use this information to design effective and translatable screening interventions.

We hypothesize that:

a) Patient self-management behavior and health care access factors are both positively associated with receipt of screening tests.

b) Health care access factors will have a stronger influence on screening than patient self-management behaviors.

2b. To identify the role of underlying health status, specifically the clinical risk of developing complications, and use of screening tests to detect complications.

Poor blood lipid, blood glucose, and blood pressure control have all been linked to the development of diabetes complications. Individuals with poor management practices in these areas are at a higher risk for developing complications, and therefore a key group of patients to screen for complications.

A) We hypothesize that individuals with higher clinical risk for developing complications will be more likely to receive screening tests than those at a lower clinical risk.

7.0 Article One: Influences on Screening for Chronic Diabetes Complications in Type 1 Diabetes

Influences on Screening for Chronic Diabetes Complications in Type 1 Diabetes

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7.1 Abstract

Purpose: Screening for the long-term complications of diabetes is a critical component of diabetes management; however, evidence demonstrates that screening rates in diabetes populations are sub optimal. Our objective was to determine the use and predictors of optimal screening behavior, defined as receiving a fasting lipid test, dilated eye exam, spot urine test, foot examination, blood pressure reading and HbA1c in the previous year in a representative cohort of subjects with type 1 diabetes (T1D).

Methods: Data are from the Pittsburgh Epidemiology of Diabetes Complications Study; a prospective cohort study of subjects with childhood onset T1D. Data from 325 participants responding to a survey during 1999-2001 were included in analyses.

Results: Reported screening rates were as follows: 87.9% had at least one HbA1c measurement in the past year, 63% had a foot exam, 73.3% had a spot urine test, 81.9% had a dilated eye exam, 93.5% had a blood pressure reading and 68.7% received a fasting lipid profile. Within this group, 37.7% of subjects reported undergoing all five tests (optimal screening). Independent correlates of optimal screening were receiving care from a specialist provider (OR=2.4, 95%CI: 1.4-4.1) and blood glucose monitoring at least weekly (OR=2.6, 95% CI: 1.1-6.2).

Conclusions: These findings indicate that a large proportion of persons with type 1 diabetes are not being screened at the optimal level. Our data indicate that efforts to rectify this should focus on men, those who do not monitor blood glucose and should involve primary care practitioners.

7.2 Introduction

Persons with diabetes are at an increased risk for vascular complications, in particular nephropathy, retinopathy, neuropathy, and coronary heart disease.[1-4] Screening practices to detect the early stages of these complications in diabetes are effective and recommended as a part of evidence based guidelines. Available tests are safe and at reasonable cost. Treatment options are available to deter the development of complications in individuals who screen positive.[1,5-8] Early detection and treatment of complications reduces adverse events associated with these microvascular and macrovascular complications in both type 1 and type 2 diabetes.[1,5-9] Therefore, utilization of all screening tests for vascular complications by diabetes patients is an important process of diabetes care.

The American Diabetes Association (ADA) recommends that persons with type 1 diabetes receive an annual dilated eye exam, foot examination, microalbuminuria screening, blood lipid tests and up to quarterly HbA1c tests, in an effort to reduce the impact of complications.[10] Although these guidelines are based on clinical evidence and accepted by the medical community, it has been reported that few obtain all recommended screening tests.[11,12] Appropriate diabetes management involves screening for chronic complications; thus investigating and addressing deficits in screening is vital in developing and maintaining quality diabetes management programs.

Although the literature describes the benefits of early detection for both type 1 and type 2 diabetes populations, screening practices have rarely been categorized in this manner. Previous research examining screening practices in diabetes has focused primarily on persons with type 2 diabetes or individuals enrolled in defined insurance plans.[11] Screening practices among persons with type 1 diabetes, are not yet fully understood. Type 1 diabetes patients are young

and in the productive phase of their lives, and evidence suggests they may have more severe disease than type 2 diabetes patients.[13]

Therefore, this study investigates the frequency of and correlates for the use of screening tests to prevent diabetes complications in a population based cohort of individuals with type 1 diabetes. The report presents findings related to the use of specific screening tests and examines factors associated with optimal screening practices.

7.3 Methods

A cross-sectional study design was used to assess; (1) the frequency in which screening tests are used in a type 1 diabetes population, and (2) the factors associated with screening. This report is based on the experiences of 325 participants identified from the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study. These individuals were identified from the Children's Hospital of Pittsburgh Type 1 Diabetes Register.[14] This register lists all persons diagnosed with type 1 diabetes during childhood before age 17 between the years 1950 and 1980. All persons were on insulin at diagnosis and seen at the Children's Hospital of Pittsburgh within one year of diagnosis. The EDC study is investigating the prevalence, incidence and risk factors for diabetes complications in type 1 diabetes.[15]

In 1999-2001, a self-administered survey was completed by the EDC participants. The survey addressed several issues, including health care access, use of health care services, health status, and screening for diabetes complications. Screening tests assessed included the fasting blood lipid profile, dilated eye exam, urine protein analysis (by spot urine or timed urine test), foot examination (by visual exam or monofilament test), HbA1c, and blood pressure reading. Respondents were asked to indicate in a yes/no fashion if they had received any of these tests at

least once in the previous 12 month period. Only screening tests obtained outside of the EDC Study were considered in the evaluation.

Potential correlates of screening were investigated, including the type of physician seen (generalist, diabetes specialist), number of doctor visits, duration of diabetes, health insurance status, self-reported presence of diabetes complications, gender, employment status, education level and diabetes self-management practices. Insurance information was captured in three ways: 1)current insurance coverage (yes/no), 2) type of insurance, including Medicaid, Medicare and private plans and 3) type of coverage, including, HMO, PPO/POS, and governmental plan. Subjects were categorized as having generalist care if their usual health care provider was a general practitioner, family practitioner, internist, nurse practitioner or physician assistant working with a generalist. Persons were categorized as having specialist care if their usual health care provider was a diabetologist, endocrinologist, nurse practitioner, or physician assistant working with a diabetologist or endocrinologist.

Self-reported diabetes complications included the presence of proliferative retinopathy or diabetic eye disease requiring laser therapy, myocardial infarction, stroke, diabetes-related renal failure, or amputation (yes/no). Study subjects were considered employed if they reported working (full or part time). Education level was dichotomized into high school education or less and at least some education beyond high school. Diabetes self-management was assessed through three variables; weekly blood glucose testing (number), changing insulin in response to blood glucose levels (yes/no) and changing diet or exercise in response to blood glucose (yes/no).

The analysis considered screening from two perspectives; the use of (A) individual screening tests, and (B) screening practices at the optimal level. Participants who indicated that

they had at least one HbA1C test, a dilated eye exam, a urine protein test, a foot exam and a fasting lipid test in the last year were defined as obtaining appropriate and optimal screening. These criteria are similar to the recommendations of the ADA, except that we used receipt of at least one HbA1c test in a 12 month period rather than two as recommended by the ADA for the study period.[10] This was done to reduce recall bias in the number of HbA1c tests conducted. In addition, if individuals were not eligible for a specific screening test (e.g. had end stage renal disease or blindness in both eyes) they were counted as having satisfied the criteria for that specific test. The impact of this consideration was small, as only 23 individuals had either end stage renal disease or blindness.

In the statistical analysis, frequencies were identified for the use of individual screening tests and screening at the optimal level. The number of specific tests received in the previous year was also examined. Chi-square and t-test statistics were used to test associations between demographic and clinical factors and the use of screening tests. Step-wise logistic regression analysis was also used to assess the strength of the association between health care, self-care and demographic factors and the use of screening tests. In this assessment, the use of the individual test (yes/no) or the use of optimal screening (yes/no) was considered as the dependent variable. The logistic regression models were built by including the explanatory variables significant univariately at the $p \leq 0.05$ level as independent variables. Variables identified in the literature as being associated with diabetes care, including diabetes duration, were also added to examine if these variables influenced the model.

7.4 Results

The mean (SD) age of the study cohort was 39.9±7.8 years, with a slight majority of the participants being female (56.0%). Mean disease duration (SD) was 31.4±7.7 years. The majority of the group reported having full year health insurance coverage (95%) and seeing a specialist as their usual source for diabetes care in the past year (65.0%). Additionally, a large proportion of participants reported at least one advanced diabetes complication (48.9%) (Table 4).

Screening Frequency and Characteristics

The use of screening tests reported by the respondents is illustrated in Figures 1 and 2. Among the individual screening tests, rates of use varied from 63% for a foot exam to 93.5% with at least one blood pressure measurement. When evaluating the optimal use of screening, only 37.7% reported the use of all recommended screening tests. Thus, 62.3% of the cohort did not report an optimal level of screening.

Associations between Covariates and Screening

Factors related to the use of each screening test were investigated and are shown in Table 5. Specialist care was significantly associated with greater use of all screening tests. Women were more likely to obtain screening tests compared to men. Changing insulin in response to blood sugar levels was associated with greater reported use of lipid profile, HbA1c, and blood pressure measurements. Testing blood sugar weekly was associated with greater use of a urine protein test. Use of specialist care and testing blood sugar at least weekly were both associated with optimal testing frequency.

Logistic regression was used to create models for individual tests and optimal screening. (Table 6) Specialist care and changing insulin in response to blood sugar level were identified as

positively associated with receipt of fasting lipid test. A positive relationship was observed between urine protein testing and specialist care, testing sugar weekly and female gender. For receipt of at least one HbA1c test, specialist care, changing insulin in response to blood sugar and female gender were most strongly associated. Changing insulin in response to blood sugar levels, the presence of health insurance coverage, and specialist care were associated with blood pressure measurement. Foot examination was directly correlated with specialist care. Finally, receipt of dilated eye exam was positively associated with specialist care, and having health insurance. When evaluating the optimal use of screening, only about one third of the cohort received an optimal level of screening. Use of specialist care and testing blood sugar weekly were both associated with receipt of optimal care. All models were adjusted for disease duration. Other potential confounding variables were explored, including diabetes complication status, which is a clinical indicator to have a test performed, education level (proxy for socioeconomic status), and insurance status. These variables, however, were not significant and did not significantly change model estimates.

7.5 Discussion

In this study, we investigated a fundamental element in the quality of care provided to persons with Type 1 diabetes; the use of screening tests for the prevention of diabetes complications. This study found that the use of screening measures varies widely. While large numbers of subjects reported receiving a HbA1c test or dilated eye exam, fewer had received a foot exam, or an assessment of blood lipids and urine protein. Only 38% of the study population reported receiving all recommended screening tests. Enhanced use of screening practices was strongly and positively correlated with seeing a physician specialist in diabetes care and greater participation in self-management practices.

These findings are the first comprehensive data available on screening practices in a large epidemiologically representative population of persons with type 1 diabetes. Previous reports have focused on screening practices in persons with type 2 diabetes or those enrolled in defined managed care health plans. In these studies, the percentage of persons receiving individual screening tests was similar to those noted in this report.[11,16-17] Glasgow, for example reported annual screening rates of 88% for HbA1c, 81% for dilated eye exam, 73% for foot exam, 73% for urine albumin test, and 91% for lipid profile in a survey of primary care patients.[16] Another study reported roughly similar findings.[17] Analysis of the 1994 BRFSS data revealed that among type 1 diabetes patients, 63.6% had a foot exam and 74.9% had a dilated eye exam.[11]

The level of optimal use of screening in this report, 38%, however, was much higher than that noted in other studies.[11-12, 18-19] Ahluwalia, for example, reported the prevalence of optimal screening among persons to be 17%.[18] Beckles, et. al. found that only 3% of insulin users met the American Diabetes Association standards for preventive care.[11] In a study conducted by Gregg, et al., only 18% of diabetes patients received all recommended preventive care services.[19]

In general, the differences seen in optimal screening practices in this report and the literature may be explained by two factors. First, as mentioned, the previous reports were based largely on the experiences of persons with type 2 diabetes. Second, differing criteria to categorize the optimal level of screening were used in the reports. Despite these differences, however, the current report and previous reports all indicate that large proportions of the diabetes population are not receiving optimal levels of screening.

The use of a specialist physician for diabetes treatment was related to the use of screening tests in this population. Specialist care was consistently correlated with better screening practices, with respect to each individual screening test, screening at an optimal level, and the

change in screening practices over time. These results are consistent with earlier data from the Pittsburgh EDC cohort which found that patients receiving care from a specialist were more likely to report HbA1c testing and dilated eye exams.[20] The current report expands upon this work to show that specialist care also influences urine protein, foot exam, and lipid testing, as well as the optimal use of screening. Other reports also suggest that process delivery is better among persons who receive care from a diabetes specialist, including control of blood pressure, foot ulcers, and infection.[20-23] Despite these findings, it is important to point out that over 30% of our population did not receive care from a specialist. Moreover, many type 1 diabetes patients rely on primary care practitioners for all of their diabetes care. Thus, these data particularly highlight the need to increase the use of screening tests among patients in primary care settings. Future actions might include the enhanced implementation of disease management programs in primary care settings, and/or the use of ancillary personnel with expertise in diabetes.

Patient behaviors, as evidenced by diabetes self-management practices in this report, may also play a role in explaining the use of screening tests. Self-testing of blood sugar and changing insulin in response to blood sugar testing were positively associated with greater use of screening in this population. This finding was independent of the role of diabetes specialist care. A study conducted by the Department of Veteran Affairs also found that self-care was associated with receipt of HbA1c tests, eye exams and nephropathy exams.[24] This relationship with enhanced diabetes self-management practices may reflect greater patient involvement in requesting screening, as well as higher levels of diabetes education received in this group.

Gender was also found to be associated with receipt of screening tests, with women more likely to obtain recommended testing. Hjelm and colleagues also found female diabetes patients to be more active in self-care and preventive care.[25] This finding may reflect the common

gender difference observed in the use of health care services, in general, and diabetes care services, in specific. It also highlights the need to further identify the reasons why men have lower rates of screening than women.

Given the design of the study, it was not possible to reliably document whether these subjects were given care under existing diabetes management programs. We assessed participation in an HMO plan in the analysis as a proxy to consider the possible influence of existing disease management programs on screening practices. While, overall, screening practices were better among HMO participants, the differences did not reach statistical significance.

The findings observed may also be influenced by bias in the study design. For example, the screening data are based upon participant self-report. It is possible that participants may not accurately recall all care received, and it was not possible to validate this data. Although for the present study, we were unable to validate self-report data, a study conducted by Fowles and colleagues assessed the validity of self-reported disease management data among diabetes patients and found that self-report data is likely to overestimate eye examination and HbA1c testing.[26] Thus, if these findings were applicable to this study, it is possible that our estimates for screening may be high. The influence of diabetes complications may also be misclassified; as our classification of complications was self-reported and may underestimate the influence of less severe complications on screening practices. We compared the self-reported complication data on retinopathy in this study to previous clinical exam findings collected as a part of the EDC study in 1998. The correlation coefficient between the two methods of identifying complications was 0.85, suggesting that the potential bias related to complications may be small. There is also

the potential for selection bias in the findings, as all subjects were participants in the longitudinal EDC study. Their patterns of care may have been influenced by this involvement.

Survivor bias may also affect the data reported. Several participants in the original EDC cohort have passed away or have become too ill to participate. It is possible that individuals remaining in the study may have enhanced screening and preventive health practices. This would mean that the screening prevalence findings may be higher than what would be expected in the general population. Therefore, these findings should only be generalized to type 1 diabetes patients of similar age and disease duration.

In summary, we found that optimal screening practices are received by about 38% of the type 1 diabetes population. Optimal screening was strongly related to the use of specialist care for diabetes treatment and diabetes self-management practices. The data in this report thus indicate a need for improved screening awareness in primary care and a focus on enhancing screening practices among males and persons not regularly testing their blood glucose. The findings of this study can be used to improve screening rates and shape disease management programs, particularly in primary care, for diabetes patients.

Screening is a critical component of diabetes disease management. The prevention of late stage complications through appropriate utilization of processes of care is an important aspect of any comprehensive diabetes management program. Measurement and evaluation of screening practices for diabetes patients, the fundamental purpose of this research, provides important information that can be used to develop diabetes management strategies. In this report, we found that screening practices among persons with type 1 diabetes who use primary care providers is particularly poor. Future disease management efforts should be focused on these individuals.

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Table 4. Demographic Characteristics of the Study Participants, 1999-2001[†]

Characteristic	Number	Percent
Gender		
Male	143	44.0
Female	182	56.0
Education		
High School Graduate or less	199	61.2
Post high school training	126	38.8
Insurance		
None	12	3.7
Public	50	15.6
Private	259	80.7
Insurance Plan		
HMO	162	50.6
PPO/POS	122	38.1
Other	36	11.3
Specialist care		
Yes	210	65
No	113	35

Table 4. (continued)

Diabetes Complication		
Yes	158	48.9
No	165	51.1
Change insulin in response to blood sugar level		
Yes	257	82.1
No	56	17.9
Weekly blood glucose testing		
Yes	252	78.3
No	70	21.7

†- Due to missing data, all columns may not add up to the total N (325)

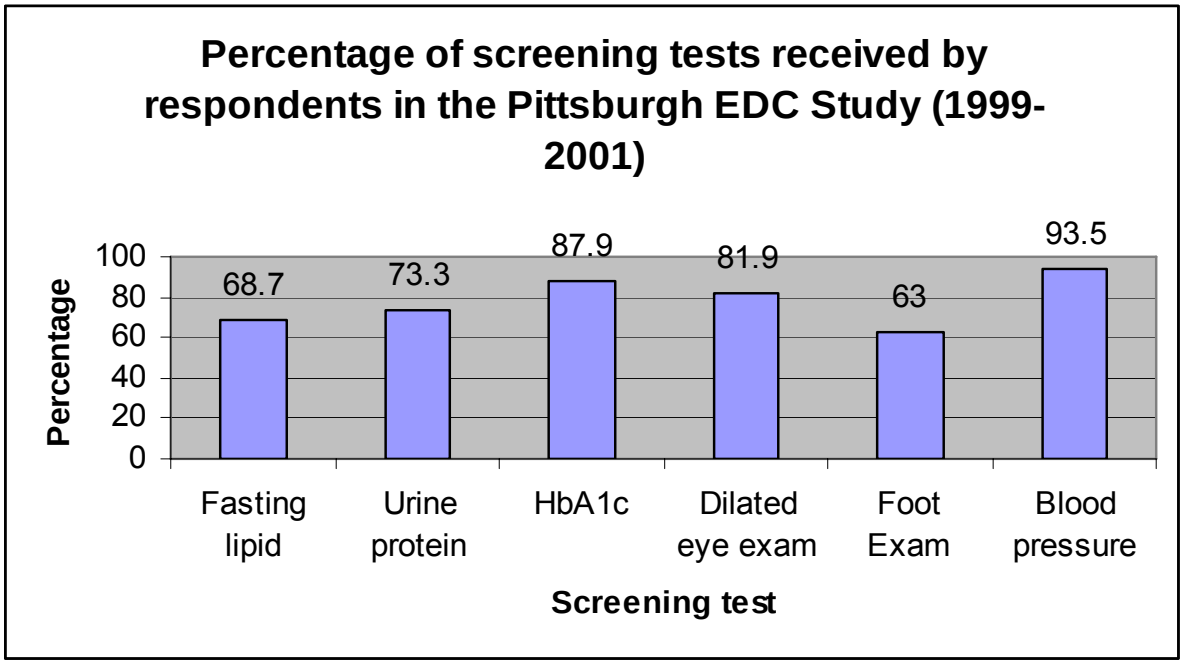

Figure 1. Percentage of Screening Tests Received by Respondents in the Pittsburgh EDC Study (1999-2001)

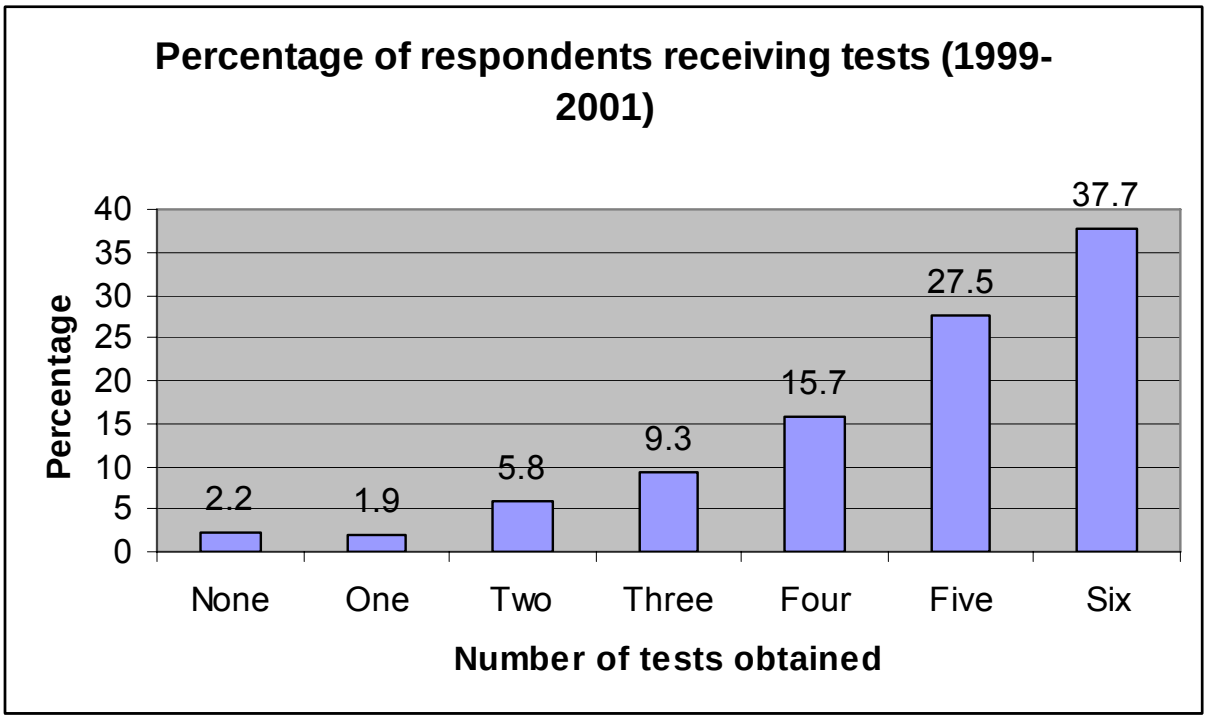

Figure 2. Percentage of Repondents Receiving Tests (1999-2001)

Table 5. Percent of Subjects Reporting Screening by Demographic and Health Care Characteristics

Characteristic % Receiving test (N)	Fasting Lipid Test	Urine Protein Test	HbA1c Test	Dilated Eye Test	Foot Exam	Blood Pressure Measurement	Optimal level screening
Gender							
Male	65.5 (93)	63.1 (89)‡	80.1 (113)‡	76.6 (108)*	57.7 (82)	90.1 (128)*	30.2 (42)*
Female	71.2 (126)	81.2 (147)	93.9 (169)	86.1 (155)	67.2 (121)	96.1 (174)	40.7 (76)
Education							
High school graduate or less	67.2 (131)	69.0 (136)*	86.2 (169)	82.1 (161)	63.8 (125)	92.4 (182)	35.3 (67)
Post high school training	71.0 (88)	80.0 (100)	90.4 (113)	81.6 (102)	61.9 (78)	95.2 (120)	41.5 (51)
Presently Employed							
Yes	68.9 (151)	71.6 (159)	88.2 (195)	79.3 (176)	59.3 (131)*	92.3 (205)	36.0 (77)
No	68.0 (68)	77.0 (77)	87.0 (87)	87.9 (87)	71.3 (72)	96.0 (97)	41.4 (41)
Insurance-HMO Plan							
Yes	69.4 (108)	75.2 (121)	91.2% (145)	83.1 (113)	64.0 (103)	95.7 (155)	39.0 (60)
No	68.4 (109)	72.6 (114)	85.4% (135)	85.2 (104)	63.1 (99)	91.1% (143)	37.4 (58)
Specialist care							
Yes	75.2(155) ‡	80.5 (169)‡	95.7 (200)‡	89.5 (187)‡	69.9 (146)‡	97.1 (204)‡	44.8 (91)‡
No	56.3 (63)	59.5 (66)	73.0 (81)	67.6 (75)	50.0 (56)	86.6 (97)	23.9 (26)
Diabetes Complication							
Yes	69.3 (106)	76.8 (119)	88.5 (138)	81.8 (126)	64.4 (105)	96.2 (150)	37.1 (59)
No	67.9 (110)	69.9 (114)	87.0 (140)	82.2 (134)	61.9 (96)	90.8 (148)	38.7 (58)

Table 5 (continued)

Change insulin in response to blood sugar level							
Yes	71.5 (181)*	76.9 (196) †	91.3 (232)†	83.5 (213)	65.6 (168)	96.1 (246)‡	40.8 (102)†
No	54.4 (30)	55.4 (31)	75.0 (42)	74.5 (41)	52.7 (29)	82.1 (46)	21.2 (11)
Weekly blood glucose testing							
Yes	71.6 (197)†	77.3 (214)‡	89.9 (248)†	83.7 (231)*	65.0 (180)	95.7 (266)*	40.7 (110)†
No	50.0 (21)	48.8 (21)	74.4 (32)	69.8 (30)	53.5 (23)	79.1 (34)	19.5 (8)

*p≤ .05

†p≤ .01

‡p≤ .001

Table 6. Models with predictors of individual screening test and optimal screening*

Screening variable	Model Covariates	OR	P-value	95% Confidence Interval
Fasting lipid profile	Specialist care	2.4	.001	1.4, 4.0
	Changing insulin in response to blood sugar levels	1.9	.048	1.01, 3.48
Urine protein test	Specialist care	2.4	.002	1.4, 4.04
	Testing blood sugar weekly	2.8	.005	1.4, 5.6
	Female gender	2.2	.003	1.3, 3.8
HbA1c	Specialist care	6.2	<.001	2.7, 14.1
	Changing insulin in response to blood sugar levels	2.6	.021	1.2, 5.8
	Female gender	2.8	.012	1.2, 6.1
Foot exam	Specialist care	2.2	.006	1.3, 3.8
Blood pressure measurement	Health insurance (yes/no)	4.3	.042	1.05, 17.5
	Changing insulin in response to blood sugar levels	4.2	.004	1.6, 11.3
	Specialist care	3.5	.019	1.2, 9.8
Dilated eye exam	Specialist care	3.6	<.001	1.9, 6.7
	Health insurance (yes/no)	5.8	.002	1.9, 17.6
Optimal screening	Specialist care	2.4	.001	1.4, 4.1
	Testing blood sugar weekly	2.6	.031	1.1, 6.2

*All models have been adjusted for disease duration

8.0 Article Two: Does Patient or Access Factors have the Largest Influence on Screening? A look at Screening Practices over time in the Pittsburgh Epidemiology of Diabetes Complications Study

Does Patient Behavior or Access Factors have the Largest Influence on Screening? A Look at Screening Practices over Time in the Pittsburgh of Diabetes Complications Study

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8.1 Abstract

Objective: Disease management incorporates patients, provider, and health care system inputs. Screening tests to detect chronic complications is an essential component of diabetes management, and diabetes is dependant upon a combination of these factors. The objective of this research was to examine screening practices over time in a well defined cohort of type 1 diabetes patients and to explore whether patient, provider or health care system factors have the strongest influence on screening behavior.

Research Design and Methods: Data are from the Pittsburgh Epidemiology of Diabetes Complications Study; a prospective cohort study of subjects with childhood onset T1D diagnosed between 1950 and 1980 and first seen in 1986-1988 (mean age 28 years, diabetes duration 19 years). Self-report data comes from surveys collected at three different time points, 1998-1999, 1999-2001 and 2002-2004 (N=334 at baseline).

Results: There was a significant trend of increasing screening rates for all screening tests, which included a fasting lipid profile, dilated eye exam, urine protein screen, blood pressure reading, foot exam, and at least 2 HbA1c tests. Screening was most often associated with access factors, specifically specialist care, number of doctor visits, and intensive insulin therapy. Receipt of recommended tests was also associated with the patient-level factor of daily blood sugar testing.

Conclusions: The findings of this report show that access factors may play the largest role in the utilization of recommended screening tests. These data imply that disease management strategies aimed at increasing screening should have a strong focus on access related factors.

8.2 Introduction

Diabetes remains one of the most significant chronic illnesses affecting the U.S. population, in terms of the number of people affected, related health care expenditures, and associated morbidity and mortality.[1,2] Diabetes patients are at risk for developing chronic complications, including nephropathy, retinopathy, neuropathy, peripheral vascular disease, and cardiovascular disease.[2] Screening tests to detect early forms of these diseases are available, and routine screening for complications is widely recommended.[3] However, despite the fact that screening for these conditions is recommended as a part of quality care, few diabetes patients receive all recommended screening tests.[4-9]

Diabetes is unique, in that the majority of disease management rests with the patient. Maintaining and monitoring glycemic control is an essential daily component of diabetes management. Adherence to diet, exercise, and prescribed medications, is an integral part of self-management and glycemic control and patients are encouraged to be diligent in this area.[3] In the case of screening for diabetes complications and sub-clinical disease, external factors play a larger role in determining adherence to recommended guidelines.

Optimal diabetes management relies on a combination of patient, provider and health care system factors.[10] Randomized trials have documented that multifaceted diabetes management programs incorporating patient, provider, and health care system factors are effective in improving glycemic control, monitoring lipid concentrations, and screening for diabetic retinopathy, foot lesions, peripheral neuropathy, and proteinuria.[10] Disease management is predicated on promoting patient self-management and physician adherence to evidence-based guidelines, and a health care system that facilitates these activities. Interventions that incorporate components such as provider feedback, provider education, provider reminders,

patient education, patient reminders, and patient and provider financial incentives have been associated with provider adherence to recommended guidelines and improved patient outcomes.[11] Additionally, interventions that address health care system factors and incorporate central computerized tracking systems and computerized decision support systems for medical personnel have been linked to improvements in diabetes processes of care.[12] Screening for diabetes complications and use of other preventive services is dependant upon a combination of these factors. Receipt of screening tests to detect complications may specifically be related to patient factors such as health seeking behavior, provider factors such as specialty type, and health care system factors such as costs.

Most of the limited literature examining the joint effect of patient, provider and system factors in the context of screening for complications is randomized control trials that describe processes of care under ideal and controlled conditions and included individuals in health maintenance organizations.[10,12] Relatively fewer studies examine how these factors may impact screening in a non-controlled setting with varying insurance plans. Even fewer studies have differentiated between type 1 and type 2 diabetes patients. Secondary prevention is the main tool to reduce burden in type 1 diabetes; therefore research focusing on complications experienced by type 1 diabetes patients is extremely important.[13] It is with this in mind that we propose to look at screening practices over time in a well-defined cohort of type 1 diabetes patients. Specifically we sought to examine whether patient, provider, or system factors have the strongest influence on screening behavior.

8.3 Methods

Data from a cohort of type 1 diabetes subjects were examined at three different time points to 1) assess the frequency of screening and 2) determine how patient-related factors and health care access factors are related to screening.

The Pittsburgh Epidemiology of Diabetes Complications (EDC) study is a longitudinal study of 658 individuals identified from an epidemiologically representative cohort of type 1 diabetes subjects. These individuals were diagnosed with childhood onset type 1 diabetes between 1950 and 1980, on insulin at diagnosis and seen at the Children's Hospital of Pittsburgh within one year of diagnosis.[14,15]

Patients involved in the study were first seen in 1986, and biannually thereafter.[15] In 1998 study subjects were surveyed to obtain additional health service information. During the EDC study, participants received clinical exams. Study subjects also completed self-report questionnaires that assessed health behavior, disease management strategies, access to health care, and screening for diabetes complications and risk factors for complications. All surveys queried activities over the previous 12 month period. This report focuses on health services data collected at three time points, 1998-1999, 1999-2001, and 2002-2004.

The outcome of interest for this investigation is whether or not a screening test to detect diabetes complications or to identify markers for complication risk was received. Screening tests assessed in this evaluation included a dilated eye examination, a urine protein test (by spot urine or timed urine analyis), and a foot examination (visual or monofilament test). Tests to screen for markers of complication risk included an HbA1c test, a fasting lipid profile and blood pressure measurement. Patients were asked if they had received the above described screening tests at

least once over the previous year (twice for HbA1c). Only screening tests that were not part of the EDC study protocol were considered.

Patient behavior and health care access issues were examined as possible factors influencing use of screening tests. Patient behaviors included the self-care practices reported regarding weekly blood sugar testing, daily blood sugar testing, changing diet in response to blood sugar levels, changing insulin in response to blood sugar levels, and changing exercise in response to blood sugar levels. Respondents were asked to indicate in a yes/no fashion if they participated in any of the aforementioned behaviors, via self-report survey.

Health care access variables included provider-related and system related factors, all collected through patient self-report survey. Provider-related variables included specialist care, number of doctor visits, and intensive insulin therapy. Individuals were considered to have specialist care if their usual health care provider was a diabetologist, endocrinologist, or nurse, nurse practitioner or physician assistant working with a diabetologist or endocrinologist. Subjects with at least 2 doctor visits were considered to have the appropriate amount of doctor visits, as a minimum standard. Intensive therapy was defined as three insulin injections per day or insulin pump therapy. System related factors included report of barriers to seeing a doctor and the presence of a usual place of care when sick.

Health care use can be affected by multiple processes. Therefore we also examined several potential confounders to the patient/access and screening test link. These include disease duration, gender, health insurance status, and diabetes complications status. Insurance status was classified as having a full year of coverage or not. Self-reported complications included the presence of proliferative retinopathy or diabetic eye disease requiring laser therapy, myocardial infarction, stroke, diabetes-related renal failure or amputation.

Analysis Plan

Screening was analyzed in two ways: (1) the use of specific, individual screening tests, and (2) the use of multiple screening practices at the optimal level. Optimal screening was defined as at least two HbA1C tests, a dilated eye exam, a urine protein test, a foot exam and a fasting lipid test in the last year. Blood pressure readings were not included as a part of the optimal variable because it is typically a part of routine office visits, and were reported in the overwhelming majority of this population. If individuals were not eligible for a specific screening test (e.g. had end stage renal disease or blindness in both eyes) they were counted as having satisfied that screening criteria for the purposes of this evaluation. The impact of this consideration was small, as only 15 individuals at time one, 23 at time two, and 15 individuals at time three, had either end stage renal disease or blindness.

Analyses were conducted cross-sectionally at each time point, using SPSS 13.0. Analyses were conducted cross-sectionally because cohort subjects did not participate at each survey point and linking the data would reduce the sample size by one third. To strengthen the validity of the study, we examined three different study points, in an attempt to show consistency in findings over time. The prevalence of screening and the prevalence of screening factors were tabulated at each time point. Chi-squared tests and t-tests were used to determine associations between screening tests and factors of interest.

Models were created to examine the effect of 1) patient factors, 2)access factors and 3)combined patient and access factors. These three model types were created by analyzing variables under the respective categories individually. Logistic regression analysis was conducted with screening tests as the outcome variable. Models were adjusted for disease

duration, complications status, sex, health insurance status. Multiple logistic regression was conducted using variables significant in univariate analyses at the .05 level, starting with the variable with the smallest p-value. These models were adjusted for disease duration, gender, complications status, and health insurance status. Models were focused on patient and access factors separately and then one model that incorporated all of these factors. Variables identified in the literature as being associated with diabetes care, even if not found to be significant at the $p \leq 0.05$ level, were also added to examine if these variables influenced the model. When making models combined with access and patient level factors, the most significant variable in univariates analysis at the .05 level was added to the model, regardless of the category the variable fell under (i.e. access or patient level), and model specification continued in a step-wise manner. Due to collinearity, daily blood sugar testing and weekly blood sugar testing were not both added to models. In the case where both were significant, daily blood sugar was used in modeling because it is more clinically significant than weekly blood sugar testing.

Trends over time in the data were also analyzed in an attempt to identify any improvements in screening and to infer which factors appear to be the driving forces influencing screening. Trend test analyses were conducted using Cochran Armitage test in the Stat Exact software.

8.4 Results

There were 334 subjects available for analysis at time point one, 325 subjects available at time two and 318 subjects available at time three. Among this cohort, 24% completed one survey, 24.2% completed two surveys and 51.7% completed all surveys. When comparing subjects who completed a survey only once to those who completed a survey two or three times, persons with diabetes complications, some college training or those employed were more likely to complete only one survey point.

Demographic data for time point is provided in Table 7. At each time point, the majority reported health insurance coverage and a large portion of subjects reported at least one late stage diabetes complication. Most subjects were female at each survey point. There was a significant decreasing trend in the proportion of subjects working and those with some college education across the survey points.

Screening Frequency and Characteristics

The prevalence of screening test utilization is reported in Table 8. Overall, the prevalence of screening has increased over the three survey points examined in this report. The largest improvements appear to be related to fasting lipid testing, urine protein testing, and optimal testing. Table 9 describes the prevalence of patient and access factors reported by respondents. The prevalence of patient behavior factors, such as daily and weekly blood sugar testing is increasing over time. More subjects also reported a usual source of care over time.

Univariate analyses were conducted between correlates and screening tests. After adjusting for health insurance, diabetes complications, gender, and disease duration, many correlates were individually found to be associated with screening. Overall, daily blood sugar testing, two doctor visits, intensive therapy, and specialist care were most frequently found to be

associated with screening in adjusted single and multiple regression analyses. A summary of those findings is presented below.

Associations between Covariates and Screening

Daily blood sugar testing, two doctor visits annually, and specialist care were associated with receipt of at least 2 Hba1c tests for all time points: time one (OR=2.1, p=.004; OR=8.1, p<.001; OR=205, p<.001, respectively) time two (OR=2.4, p=.033; OR=11.2, p<.001; OR=5.1, p<.001, respectively) and three (OR=2.3, p=.025; OR=6.7, p<.001; OR=2.8, p<.001, respectively). Weekly blood sugar testing was associated with Hba1c testing at time three (OR=3.2, p=.019), and intensive therapy was associated with receipt of the screening test at both time one (2.3, p=.001) and time three (2.8, p=.002). Changing insulin (OR=2.1, p=.008), diet (OR=2.0, p=.007), and exercise (OR=1.9, p=.015) in response to blood sugar level were each associated with screening at time one.

Two doctor visits was associated with receipt of a fasting lipid test at time point 1 (OR=3.8, p<.001), time two (OR=3.9, p<.001) and time three (OR=4.3, p<.001). Weekly blood sugar testing was positively associated with fasting lipid testing at time two (OR=2.5, p=.009) and daily blood sugar testing was associated at time two (OR=2.7, p<.001) and three (OR=2.4,p=.01). Fasting lipid testing was associated with specialist care at time two (OR=2.3, p=.001) and time three (OR=4.2,p<.001).

Receipt of a dilated eye exam was associated with weekly blood sugar testing at time point three only (OR=2.9, p=.026). At time point one, two doctor visits (OR=3.2, p<.001), intensive therapy (OR=2.3, p=.007), and specialist care (OR=2.4, p=.002). Likewise at time two, these same access factors were found to be associated with screening: two doctor visits (OR=2.2, p=.022), intensive therapy (OR=2.0, p=.031), and specialist care (OR=3.6, p<.001).

Subjects reporting a foot exam were more likely to report weekly blood sugar testing at time three (OR=3.4, p=.003). Two doctor visits was positively correlated with screening at time one (OR=4.0, p=.001) time two (OR=2.1, p=.001) and time three (OR=2.8, p=.002). Daily blood sugar testing was associated with foot examination at time two (OR=2.1, p=.009) and time three (OR=2.2, p=.014). At time points one and two, intensive therapy was associated with receipt of a foot exam (OR=2.4, p=.006; OR=1.8, p=.017, respectively). Specialist care was associated with this screening test at time two (OR=2.2, p=.002) and time three (OR=2.9, p<.001).

Respondents indicating they had received a urine protein test in the past year were more likely to report weekly blood sugar testing at time two (OR=3.3, p=.001) and time three (OR=2.9, p=.009). Changing insulin in response to blood sugar levels was associated with receipt of urine protein test at time two only (OR=2.5, p=.005). Daily blood sugar testing was positively associated with urine protein testing at time two (OR=3.6, p<.001) and time three (OR=3.4, p<.001). Two doctor visits was associated with urine protein screening at all time points; time one (OR=4.4, p<.001), time two (OR=4.0, p<.001) and time three (OR=4.7, p<.001). Additionally, intensive therapy was associated with this screening test at all three points; time one (OR=2.4, p<.001), time two (OR=1.9, p=.023) and time three (OR=2.3, p=.006). Finally, specialist care was associated with urine protein testing at all three survey points; time one (OR=3.8, p<.001), time two (OR=2.4, p=.002) and time three (OR=3.9, p<.001).

Optimal screening was associated with two doctor visits at time point one (OR=6.2, p=.001) time two (OR=10.3, p=<.001) and time three (8.0, p<.001). Weekly sugar testing was associated with optimal testing at time two (OR=2.7, p=.018) and time three (OR=2.6, p=.03). Additionally, daily blood sugar testing was associated with optimal screening at time two (OR=2.3, p<.001) and time three (OR=2.5, p=.006). Changing insulin in response to blood sugar

levels was associated with receipt of optimal screening at time two only (OR=2.5, p=.014), and intensive therapy was associated with the test at time three only (OR=3.6, p<.001). Lastly, specialist care was associated with optimal testing at all three time points; one (OR=3.0, p<.001), two (OR=2.3, p<.001) and three (OR=3.1, p<.001).

Final multiple regression models, using patient level factors, access factors, and combined patient and access factors were created. There were no final models exclusively comprised of patient level factors. Final access models are presented in the Table 10. Combined models for urine protein testing, optimal testing and Hba1c testing for time points two and three are presented in table format (Table 10). The only combined model for time point one was for HbA1c testing, where changing exercise in response to blood sugar levels (OR=2.2, p=.017; 95% CI=1.2,4.1), intensive therapy (OR=2.1, p=.019; 95% CI=1.1, 3.9) and two doctor visits (OR=8.4, p<.001; 95% CI=4, 18) were associated with screening after adjusting for disease duration, gender, complications and insurance status. There were no combined models for dilated eye examination at any time point. For time point two, the final combined model for fasting lipid test consisted of two doctor visits (OR=3.7, p<.001; 95% CI=2.0, 6.8) and daily blood sugar testing (OR=2.5, p=.002; 95%CI=1.4, 4.5). These same factors made the final combined model for foot examination for survey point two; two doctor visits (OR=2.0, p<.001; 95% CI=1.1, 3.6) and daily blood sugar testing (OR=1.8, p=.048; 95%CI=1.0, 3.1).

8.5 Discussion

In this study, we examined the relationship between patient-level factors and access factors, and receipt of screening tests. This association was investigated using three sets of cross-sectional data, collected from a cohort of type 1 diabetes subjects participating in a prospective cohort study. The data show that screening rates appear to be improving over time. At time one, the screening prevalence for individual tests varied greatly (range 51.5% for urine protein test to 84% for blood pressure exam [81.1% dilated eye]), but this difference was lessened over time as screening rates improved (range 73.1% for foot exam to 94.9% for blood pressure measurement [87% dilated eye]). Screening was most often found to be associated with access factors, specifically specialist care, number of doctor visits, and intensive insulin therapy. Receipt of recommended tests was also associated with the patient-level factor of daily blood sugar testing.

These findings among subject with type 1 diabetes agree with prior results reporting screening rates among both type 1 and type 2 diabetes patients.[7,9,16-17] For instance, Kaiser Permanente analyzed administrative databases and found that screening rates for HbA1c, urine protein, and lipids improved between 1994 and 1997.[9] Similarly, national data from the Behavioral Risk Factor Surveillance System showed screening rates for both dilated eye and foot examinations have increased for diabetes patients.[17]

In this study we also found significant trends in patient level and access level factors, specifically daily blood sugar testing and intensive therapy. These factors were found to be significantly associated with the different screening tests at each time point, suggesting there may be a correlation between improvements in these factors and improvements in screening. We also found that several access factors are consistently associated with receipt of screening tests at the different time points: intensive therapy, specialist care, and two annual doctor visits.

Intensive therapy, which we defined as three insulin injections per day or insulin pump use, was found to be associated with screening tests. Intensive glycemic control has been linked to improvements in diabetes outcomes, and here it is associated with improvement in processes of care.[18]

Another finding of our study was the strong correlation between specialist care and the receipt of all screening tests and multiple time points. Previous studies have linked specialist care to higher screening rates among diabetes patients and general improvements with diabetes outcomes. Specifically, specialist care has been linked to improvements in blood pressure management, foot ulcers, infection, and screening for complications. These data provide additional evidence of the utility of specialty care.[19-21]

Along with intensive therapy and specialist care, visiting a physician at least two times per year was also positively associated with each screening tests at almost every time points. These data reaffirm the notion that physician care plays an integral role in chronic disease management, and these data provide more evidence of that. For instance, Cook et al found that quarterly physician visits were associated with higher rates of foot examination.[22] Likewise, a recent study conducted by Hensley et al found improvements in intermediate outcomes such as blood pressure measurement, lipid levels and HbA1c level correlated with increasing visits to a health care provider.[23] Gary et al also found that patients more likely to have at least four physician visits per year had higher rates of HbA1c testing.[24]

Research has often found a link between the presence of health insurance coverage and use of health services.[4] In our sample, over 95% of subjects reported health insurance coverage. Additionally, the few individuals reporting lack of coverage often reported receiving screening tests. Thus, due to very small cell sizes, health insurance coverage was controlled for instead of

testing for associations between coverage. This methodological approach is in line with other research investigating use of screening tests in population based cohorts, where adjusting for the presence of health insurance coverage is often done.[4, 5]

In our study, daily blood sugar testing was the only patient-level factor associated with many screening tests at different time points. Self-monitoring of blood glucose and maintaining appropriate glycemic control is a critical component of diabetes management. It is possible that patients who test their blood sugar daily are in more control of their disease, and more likely to be proactive in other areas of management. Day et al found that individuals with better glycemic monitoring and control had higher levels of self-efficacy, emotional adjustment to disease and practical self management skills.[25] Patient characteristics that confer self-monitoring of blood glucose may also lead patients to obtain screening tests.

In our data, access level factors appear to have a greater affect on screening than patient level factors. The observed relationship between access factors and screening is plausible because research examining factors related disease management have consistently shown physician and system level variables associated with optimal care. Our findings must be interpreted with a degree of caution, as patient, provider and system factors are not independent, and work together to influence health care.[26] In this study we grouped covariates according to patient or access factor categories that largely characterize the variable, however overlap may still occur. For instance, specialist care and the number of annual doctor visits may be related to patient motivation and health-seeking behavior, in addition to provider characteristics, to influence screening behavior. Likewise, daily blood sugar testing is typically strongly encouraged by health care providers, which may have an impact on a patient's decision to monitor blood sugar daily. We explored the potential impact of patient motivation on selection

of provider type. We used the glycemic control variables of changing insulin, exercise, and diet in response to blood sugar levels as proxy variables for patient motivation and examined the relationship between choice of specialist or generalist as provider type. We found that patients who see specialists were more likely to change their insulin levels in response to their blood sugar levels. This suggests that patient motivation may influence on choice of provider type, and thus more of an influence on screening than these data capture. However, it is also possible that provider type may have an influence over patient motivation and practices towards self-management. Further exploration on the influence of patient motivation on provider type, screening, and disease management is warranted.

There are several limitations to consider when interpreting these findings. First the data are cross-sectional, which prohibits direct detection of a causal linkage. However, our data represent three separate cross-sectional analyses with similar findings, which support the validity of our findings. Additionally, all data all self-reported and subject to recall bias and we have no mechanism to validate these data. Furthermore, proxy variables were used to describe patient and access factors, as we did not directly assess these variables.

There is also the potential for selection bias, as all respondents are involved in the longitudinal Pittsburgh Epidemiology of Diabetes Complications study. Health care utilization for study subjects may differ than those of type 1 diabetes patients not participating in the study, and participation in the study may influence health care utilization. The data reported may also reflect survivor bias. Many in the original study cohort have passed away or become too ill to participate. Remaining subjects may have better disease management and higher screening rates which has allowed them to remain in the study. In this report, we examined three different survey points of data. Some participants completed all three survey points, while other

completed two or one survey point. Baseline differences between those who completed only one survey point versus those who completed two or three may be present. We found that persons with diabetes complications, some college training or those employed were more likely to complete only one survey point. This could have influenced our findings. However it should be noted that only 24% of the population completed a survey at only one time point.

In summary, diabetes management relies on patient level factors as well as provider and systems factors. Previous research that has examined the combined effect of these factors on general diabetes outcomes and processes of care has consisted of randomized trials, and the majority of these studies were not designed to examine their effect on screening practices. In addition, it has been noted that dissemination of models shown to be effective in randomized trials is often impeded by incompatibility with the health care system and a disconnect with provider practice.[27] Therefore, it is important to investigate which factors influence screening in a natural setting, amongst patients who are not privy to intervention involvement, as this likely represents a large portion of patients.

The data in this report show that access factors may play the largest role in utilization of recommended screening tests. Unlike other areas of diabetes management, such as glycemic control, these data suggest that access factors may play a larger role in driving screening than patient-level factors. The findings from this report imply that disease management strategies aimed at increasing screening should have a strong focus on access related factors.

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Table 7. Demographic Characteristics of Study Populations at Three Survey Points

Characteristic % (N)	**Time One (1998-1999) N=334**	**Time Two (1999-2001) N=325**	**Time Three (2002-2004) N=318**
Disease Duration (mean±sd)	26.9±3.9	31.7±7.7	32.6±7.4
Age (mean±sd)	37±8.8	39.9±8	41.9± 7.8
Gender (male)	49.4% (165)	44% (143)	45.2% (136)
Health Insurance Coverage	95% (95.5)	95% (306)	94.9% (296)
Diabetes Complication	44% (146)	48.4% (158)	53.8% (168)
Presently Working*	71.8% (238)	68.6% (223)	66.8% (211)
Education Level Some College	69.9% (232)	38.6% (125)	41.5% (132)

*P-value for trend <.05

Table 8. Screening Prevalence for each Survey Point

Screening test	**Time One (1998-1999) N=334**	**Time Two (1999-2001) N=325**	**Time Three (2002-2004) N=318**
HbA1c test (at least 2)*	60.5% (202)	69.9% (218)	76.2% (230)
Fasting lipid test*	55.1% (178)	68.7% (219)	77.4% (240)
Dilated eye exam*	81.1% (266)	81.9% (263)	87% (268)
Urine protein test*	51.5% (169)	73.3% (236)	73.7% (230)
Foot exam*	53.4% (101) *large amount of missing data*	63% (203)	73.1% (228)
Optimal *	25% (80) *foot exam not included C6*	30.7% (93)	44% (131)
Blood pressure**(not included in optimal)*	84% (274)	93.5% (302)	94.9% (296)

*P-value for trend <.05

Table 9. Prevalence of Patient and Access Factors for each Survey Point

Characteristic	Time One (1998-1999) N=334	Time Two (1999-2001) N=325	Time Three (2002-2004) N=318
P: Weekly blood sugar testing*	79.4% (265)	86.7% (279)	89.4% (279)
P:Daily blood sugar testing*	62.6% (249)	76.6% (249)	79.9% (239)
P:Change in diet in response to blood sugar levels*	62.3% (172)	81.9% (222)	Not asked
P:Change in exercise in response to blood sugar levels*	36.9% (206)	53.2% (141)	Not asked
P:Change in insulin usage in response to blood sugar levels*	74.4% (206)	82.1% (257)	Not asked
A: Barrier to seeing doctor (presence of a barrier)	11.2% (37)	9.0% (29)	10.4% (33)
A: Two doctor visits	78.3% (231)	79% (248)	82.7% (263)
A: Three insulin injections per day or use of insulin pump*	42.9% (142)	65.5% (205)	58.5% (186)
A: Specialist Care	61% (197)	65% (215)	65.9% (205)
A: Usual place of care when sick*	79.4 % (265)	91.4% (297)	Not asked

*P-value for trend <.05, **P**=Patient factor, **A**=Access factor

Table 10. Significant Independent Access Factors for Screening Tests at each Survey Point (Logistic Regression Models)

Test	Time One			Time Two			Time Three		
	Factor	OR	95% CI	Factor	OR	95% CI	Factor	OR	95% CI
Eye	Two doctor visits	2.9**	1.5, 5.7	Specialist	3.1**	1.6, 6.0	NM		
	Intensive therapy	2.0*	1.1, 4.0	Intensive therapy	2.1*	1.1, 4.1			
Urine	Two doctor visits	2.9**	1.5, 5.9	Intensive therapy	1.7*	1.0, 3.1	Specialist	2.9**	1.5, 5.7
	Specialist	3.1†	1.8, 5.3	Two doctor visits	3.9†	2.1, 7.2	Two doctor visits	6.6†	2.4, 18.3
Foot	Two doctor visits	3.6**	1.6, 8.4	Specialist	1.9*	1.7, 6.0	Specialist	2.9**	1.5, 5.7
	Intensive therapy	2.2*	1.1, 4.4	Two doctor visits	6.6†	2.4, 18.3	Two doctor visits	6.6†	2.4, 18.3
HbA1c	NM			Specialist	3.3**	1.8, 6.1	Specialist	3.0**	1.5, 5.7
				Two doctor visits	8.4†	4.2, 16.9	Two doctor visits	6.8†	3.1, 14.9
Fasting Lipid	NM			Specialist	1.9*	1.7, 6.0	Specialist	2.9**	1.5, 5.7
				Two doctor visits	6.6†	2.4, 18.3	Two doctor visits	6.6†	2.4, 18.3
Optimal	Two doctor visits	4.9**	1.6, 14.3	Two doctor visits	7.7**	2.3, 26.1	Intensive therapy	3.2†	1.8, 5.5
	Specialist	2.0*	1.1, 3.9	Specialist	2.6**	1.3, 5.1	Two doctor visits	6.6†	2.4, 18.3

* p<.05, ** p<.01, † p<.001

NM=no significant model found in statistical analyses

Table 11. Final Logistic Regression Combined Access and Patient Factor Models for Screening Tests for each Survey Point

Time	HbA1c combined				Optimal Combined				Urine Combined			
	Factor	OR	p-value	95% CI	Factor	OR	p-value	95% CI	Factor	OR	p-value	95% CI
Time Two	Daily blood sugar testing	2.1	.037	1.1, 4.1	Daily blood sugar testing	2.4	.025	1.1, 5.2	Daily blood sugar testing	3.3	<.001	1.7, 6.1
	Two doctor visits	10.7	<.001	5.4, 21.1	Two doctor visits	9.7	<.001	2.9, 32.5	Two doctor visits	3.7	<.001	2.0, 7.0
Time Three	Daily blood sugar testing	2.4	<.001	1.2, 6.8	Daily blood sugar testing	2.1	.03	.1, 4.1	Daily blood sugar testing	2.3	.016	1.2, 4.4
	Specialist	3.7	.01	2.0, 6.8	Specialist	2.9	<.001	1.6, 5.0	Specialist	2.9	<.001	1.6, 5.3
									Two doctor visits	3.1	.002	1.5, 6.5

9.0 Article Three: Risk for Developing Complications and use of Preventive Screening Tests in a Type 1 Diabetes Cohort

Risk for Developing Complications and the use of Preventive Screening Tests in a Type 1 Diabetes Cohort

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9.1 Abstract

Objective: Uncontrolled blood glucose, blood pressure, and blood lipid levels are associated with the development of all the major diabetes complications. Screening tests are available to test early stages of complications. Little is known about the link between risk of developing complications and use of screening tests to detect complications. The objective of this study was to examine this relationship.

Research Design and Methods: Study subjects were 260 type 1 diabetes patients involved in the longitudinal Pittsburgh Epidemiology of Diabetes Complications Study. Risk for developing complications data came from clinical examinations of subjects conducted in 1997-1998, and included HbA1c, blood pressure, and low-density lipoprotein (LDL) measurement. Subjects were classified (categorized into four levels of increasing risk, with the lowest tier the target level) as being at target for each clinical indicator, according to Joint National Committee, National Cholesterol Education Program, and DQIP standards. Screening test data came from self-report survey data collected in 1999-2000. Risk was prospectively analyzed with screening data.

Results: Few associations were observed between HbA1c levels above target, blood pressure levels above target, and LDL levels above target and use of screening tests to detect chronic complications. A positive association between LDL level above target and receipt of fasting lipid test and urine protein testing.

Conclusions: We did not find may associations between clinical risk and receipt of screening tests. This may be attributed to either that fact that: 1) screening is deemed equally valuable for all patients regardless of clinical risk or 2)patients at highest clinical risk for developing complications are not being targeted for secondary prevention. A more in-depth

review of screening practices among diabetes patients to ensure that minimally, high risk patients are involved and targeted in screening efforts is needed.

9.2 Introduction

Diabetes is associated with several late stage chronic complications that result in significant morbidity and mortality.[1] These chronic conditions include diabetic eye disease from retinopathy, kidney disease from nephropathy, foot disease from peripheral vascular disease and peripheral neuropathy and coronary heart disease. Diabetes complications are responsible for more than 200,000 deaths per year and close to 25 billion dollars in medical expenditures annually.[2]

Uncontrolled blood glucose, blood pressure, and blood lipid levels are associated with the development of all the major diabetes complications.[3-6] The landmark Diabetes Complications Control Trial (DCCT) showed that intensive glycemic control reduces the incidence and progression of microvascular complications as well as heart disease and stroke.[7] Another ground-breaking clinical trial, the United Kingdom Prospective Diabetes Study (UKPDS) found that the risk of developing coronary heart disease increased with rising blood lipid levels and blood pressure levels in a type 2 diabetes population.[8]

Several models have been developed from these trials and other studies to predict the development of late stage complications. Blood lipid concentrations, blood pressure values, and blood glucose levels are key indicators of risk in these models. Elevated mean total cholesterol, high HbA1c levels, and use of antihypertensive medications have been used in one model to predict diabetes patients at high risk for developing complications, such as proliferative retinopathy, nephropathy, heart disease and foot disease.[9] Coronary heart disease prediction algorithms have consistently found risk of developing coronary heart disease attributable to elevated blood pressure levels and elevated total cholesterol and LDL cholesterol levels.[10-12]

Thus, there is a strong body of evidence linking hyperlipidemia, hypertension, and hyperglycemia to chronic disease development.

Screening tests are available to detect the early stages of chronic diabetes complications and effective therapies exist to prevent the progression of diabetes complications, and include the dilated eye exam, comprehensive foot examination, urine protein screen.[13] There are also tests for risk factors for complications, that include the fasting lipid test and HbA1c test, and treatments for these poor control of these conditions are available as well. Routine screening for complications and risk factors for complications is recommended by the American Diabetes Association.[13] Despite the fact that the utility of screening has been shown in research, many diabetes patients do not receive appropriate screening.[14] Little is known about the risk for developing complications and use of screening practices in diabetes community.

Patients with poor glycemic, blood pressure and lipid control are at a higher risk developing complications than diabetes patients without these risk factors, and it is therefore especially important to target screening for chronic complications towards these individuals. The objective of this report is to investigate the relationship between the level of clinical risk for complications and the use of recommended screening tests for the prevention of diabetes complications.

9.3 Methods

Study Population

This report is based upon experiences reported by participants in The Pittsburgh Epidemiology of Diabetes Complications study (EDC). This sample is an epidemiologically representative sample of persons with Type 1 diabetes. Identified from the Children's Hospital of Pittsburgh Type 1 Diabetes Register, the sample consists of patients diagnosed with childhood

onset type 1 diabetes between 1950 and 1980, who were on insulin at the time of diagnosis and were seen at the Children's Hospital of Pittsburgh within one year of diagnosis.[15] The Children's Hospital registry provides a sample of patients that is representative of the type 1 diabetes population in Allegheny County, Pennsylvania.[16] The EDC study is investigating the prevalence, incidence and risk factors for diabetes complications in type 1 diabetes.

Study Design

This analysis examines the link between the risk for complications and the use of screening tests, using a prospective design. The level of risk for complications was identified from clinical examination data collected in the EDC study during a tenth year follow-up exam in the EDC cohort during 1997-1998. These data were compared to screening data collected two years later between 1999 and 2000. In the clinical exam, participants were assessed to document the presence of diabetes complications. Glycemic control, hyperlipidemia and hypertension status were also assessed during the clinical examination. In addition, participants completed a self-administered survey which identified health care access, use of diabetes related services, and health status over the previous year. In 1999-2000, subjects completed a self-report survey that addressed the use of screening tests to detect diabetes complications. A clinical examination was not conducted in 1999-2000. Thus, in this evaluation, data on risk levels has been gathered in a different fashion than the data on screening. Risk levels were determined by clinical examination; whereas screening data come from self-report of testing obtained outside of the EDC study.

Definition of Risk for Complications

The level of risk for developing complications in this cohort was defined by considering the current health of participants and their degree of disease management with regard to blood

glucose, blood pressure and blood lipids. Glycemic control was identified using the HbA1c measure. Blood pressure control was available from systolic and diastolic measurements, and lipid control was be defined on the basis of measured LDL levels. Blood pressure was measured by sphygmomanometer, according to the Hypertension Detection Follow-Up Program protocol. Low density lipoprotein (LDL) levels were calculated from measurements of the levels of total cholesterol, triglycerides, and HDL cholesterol using the Friedewald equation. HDL cholesterol was determined by a precipitation technique (heparin and manganese chloride) with a modification of the Lipid Research Clinics method. Cholesterol and triglycerides were measured enzymatically. Glycemic control was measured using HbA1 laboratory values converted to HbA1c. The conversion equation is HbA1c= .9HbA1+.05. HbA1 was measured using high-performance liquid chromatography (Diamat; Bio-Rad Laboratories, Hercules, CA).

Criteria to distinguish the level of risk associated with blood pressure, and LDL cholesterol risk were based on the threshold values determined to be clinically significant predictors of complication development in the EDC study.[17] These criteria are in accordance with the Joint National Committee (JNC-V) blood pressure and National Cholesterol Education Program (NCEP) standards.[18-19] A criterion to distinguish the level of risk related to glycemic control was adapted from the Diabetes Quality Improvement Project (DQIP) HbA1c threshold values. The blood glucose, pressure and lipid variables were each broken into four categories of risk, with high levels corresponding with higher risk of developing complications. LDL categories were defined as (from lowest level to highest level): less than 100 mg/dL, 100-129 mg/dL, 130-159 mg/dL, and greater than or equal to 160 mg/dL. Subjects on medication to control lipid levels were assigned to the highest risk category. Systolic blood pressure categories were defined as follows (from lowest to highest level): less than 110 mmHg, 110-119 mmHg,

120-129 mmHg, and greater than or equal to 130 mmHg. Diastolic blood pressure categories were as follows (from lowest to highest level): less than 80 mmHg, 80-84 mmHg, 85-89 mmHg and greater than or equal to 90 mmHg. Subjects on medication to control blood pressure were assigned to the highest systolic and diastolic blood pressure groups. HbA1c categories were as follows (from lowest to highest level): less than 8.0%, 8-8.9%, 9-9.9%, and greater than or equal to 10%.

In addition to the primary explanatory variables, three additional factors associated with the development of complications were examined. Research has shown that individuals with at least one late stage complication are at risk for developing another. Also, smoking behavior and diabetes disease duration have been linked previously to diabetes complications. As such these items were included in analyses. During the EDC clinical exam, study subjects were also assessed for the presence of nephropathy, distal symmetric polyneuropathy, retinopathy, peripheral vascular disease and coronary heart disease. Evidence for any of these conditions was used to group subjects as either having at least one late-stage complication or not. Complications were considered late-stage if the existing condition was in the latter stages, according to the natural history of the specific disease or in the tertiary preventative stage for the condition.

Distal symmetry polyneuropathy was defined as the presence of two or more of the following: symptoms consistent with DSP, decreased (i.e. requiring reinforcement) or absent tendon reflexes, and signs of sensory loss. Overt nephropathy was classified as albumin excretion ratio (AER) >200 μg/min in two of three timed urine collections or in the absence of a urine serum creatinine >5mg/dl, or renal failure or renal transplantation. Proliferative retinopathy was ascertained using stereoscopic fundus photographs graded according to the modified Airlie House System, grade ≥60. Individuals with laser therapy or blindness were also considered to

have retinopathy. Lower extremity arterial disease was classified according to resting ankle to arm ratio <0.8in any of four ratios, or positive claudication or amputation for a vascular disease. Coronary heart disease was defined as non-fatal myocardial infarction, angina, ischemic heart ECG, angioplasty, coronary end angina, thrombolysis, CABG, or stenosis ≥50%. Disease duration was identified for each patient at study baseline, and was dichotomized as either less than 25 years or greater than or equal to 25 years. Previous research in this cohort has shown that subjects with 25 or more years or disease duration were more likely to develop complications.[20] Study subjects self-reported smoking status, and those who indicated they were current smokers were classified as smokers.

Preventive Screening Practices

The use of recommended screening practices for chronic complications collected from self-report data in 1999-2000 was examined as the outcome variable. Specific tests examined included the HbA1c test, dilated eye exam, fasting lipid test, foot exam (by visual exam or monofilament test), urine protein test (by spot urine or timed urine test). Respondents were asked to indicate whether they had received any of the aforementioned tests at least once in the previous 12 month period. Only screening tests obtained outside of the EDC Study protocol were considered in the evaluation.

Study Covariates

Several covariates shown to be associated with receipt of screening tests and diabetes complications were also collected in the survey. These include the type of physician seen (generalist, diabetes specialist), number of doctor visits, health insurance status, and gender. A person was classified as having generalist care if their usual health care provider was a general practitioner, family practitioner, internist, or nurse practitioner or physician assistant working

with a generalist. A person was considered to have specialist care if their usual health care provider is a diabetologist, endocrinologist, or nurse practitioner, or physician assistant working with a diabetologist or endocrinologist. Insurance status was categorized as having full year coverage or not.

Analysis Plan

The analytic approach considered screening from two perspectives; the use of (A) individual screening tests, and (B) screening practices at the optimal level. Participants who indicate that they had at least one HbA1C test, a dilated eye exam, a urine protein test, a foot exam and a fasting lipid test in the last year were defined as obtaining appropriate and optimal screening. These criteria are similar to the recommendations of the ADA, except that we used receipt of at least one HbA1c test in a 12 month period rather than two to four as recommended by the ADA. This was done in an effort to reduce inaccuracy in the recall of the number of HbA1c tests conducted. In addition, if individuals were not eligible for a specific screening test (e.g. had end stage renal disease or blindness in both eyes) they were counted as having satisfied that screening criteria for the purposes of this evaluation.

Analytic modeling was adapted from The Cardiovascular Event Risk Reduction Tool (CERT) study. The CERT is a simplified cardiac risk prediction model derived from the West of Scotland Coronary Prevention Study (WOSCOPS) data. In CERT models, continuous risk factors for coronary heart disease (age, systolic blood pressure, diastolic blood pressure, cholesterol level) variables were expressed as categorical variables. Additional risk factors for coronary heart disease (current smoking, diabetes, family history of heart disease, and nitrate use or angina) were grouped into one composite variable, with a score from 0-4, and added to the model. Hazard models were created by adding all continuous risk factors and the additional risk

factors, as a part of the analysis plan. Risk ratios for each categorical variable level were calculated, via the use of dummy variables. The formation of key variables and regression model formation for the present study was adapted from this protocol.

Model A (Total of 4 Models)

Risk Factor (Only one per model)		+	***Additional Risk Factors (0-3)***
Systolic Blood Pressure	OR		Disease duration + Complication + Smoking
Diastolic Blood Pressure	OR		
LDL Cholesterol Level	OR		
HbA1c Level			

Model B

Risk Factor (All in model)	+	***Additional Risk Factors (0-3)***
Systolic Blood Pressure		Disease duration + Complication + Smoking
Diastolic Blood Pressure		
LDL Cholesterol Level		
HbA1c Level		

Model C

Risk Factor (All included)	+	***Additional Risk Factors (0-3)***	+	***Covariates***
Systolic Blood Pressure		Disease duration + Complication + Smoking		Specialist Care
Diastolic Blood Pressure				Health Insurance
LDL Cholesterol Level				Gender
HbA1c Level				

Figure 3. Analytic Models used in Data Analysis of Risk Factors and Preventive Care.

The outcomes for each model type are receipt of individual screening tests and optimal screening.

For the present report, the modeling plan is detailed in Figure Three. The association between risk level for developing complications and screening was examined. The clinical risk variables were categorized into four levels of increasing risk, as characterized above. Dummy variables were created and used in the analysis plan, to explore potential dose-response relationships. The analyses were conducted first examining the risk level for each factor (HbA1c, LDL, diastolic blood pressure, and systolic blood pressure) as the main explanatory variable individually and receipt of screening for individual and optimal tests. Next, a model containing all risk variables and their relationship with screening as the outcome (individual tests and optimal) was created. A composite variable consisting of disease duration, smoking status, and complication status was created to account for the effect of additional risk factors for developing complications and added to the models. All models, those examining risk variables individually as well as the combined risk models had a variable accounting for 0-3 additional risk factors. Finally, the effect of specialist care, gender, and health insurance status as potential confounders was explored. The potential confounders were added to models to examine their impact on model estimates. Due to collinearity, systolic blood pressure and diastolic blood pressure were not both included in models with multiple risk factors; only systolic blood pressure was used, largely because of small diastolic blood pressure cell sizes.

Chi-square and t-test statistics were used to examine associations between potential correlates of screening and the use of screening tests. In this assessment, the use of the individual test (yes/no) or the use of optimal screening (yes/no) was considered the outcome variable. The primary explanatory variable is risk status, determined by clinical exam. Logistic regression analysis will first be analyzed to determine the unadjusted association between risk status and additional risk factors and each screening test and optimal screening. Logistic

regression models will then be built by including the potential confounders significant at the $p \leq 0.05$ level to models.

9.4 Results

Baseline Sample Characteristics

There were 399 patients with risk variable data available for analysis from the (1997-1998) clinical exam and 325 patients with screening data available from 1999-2000. These data were linked, giving 260 subjects with linked clinical examination and screening data, and information from this linked data set is presented here. Compared to study subjects, those excluded due to lack of follow-up data were more likely to be smokers (21.7% % vs. 13.5%; p=.035) and more likely to be male (60.4% vs. 45.0%; p=.003). There were no significant differences between the HbA1c, systolic blood pressure, diastolic blood pressure, and LDL risk levels between the two groups.

The mean age for participants in the combined dataset was 37.5±8 years, and the mean disease duration was 29.3±7.5 years at baseline. Demographic data are presented in Table 12. Most participants had at least one late stage diabetes complication (64.7%) and the majority reported the presence of health insurance coverage (95.8%).

Baseline level of Risk

Figure 4 and Figure 5 show the distribution of diastolic and systolic blood pressure risk level groups, respectively. An overwhelming majority of subjects are in the lowest diastolic blood pressure risk level group (n=82.7%). In contrast there is a broader distribution of subjects in the systolic blood pressure risk levels groups. Figures 6 and 7 display the distribution of LDL and HbA1c risk level groups, respectively. For these two risk factors, there is fairly equal distribution in each of the risk groups, with the second tier having the most patients (n=

29.3%for LDL and n= 26.2% for HbA1c). Finally, the majority of subjects have two additional risk factors, as shown in Figure 8 (n=47%).

Screening Practices

In the 1999-2000 survey, the majority of group reported receiving a dilated eye exam (82.2%) and HbA1c test (88.8%) in the past twelve months. Likewise, a total of 70.3% the population reported receiving a fasting lipid test and 74% reported urine protein test. Among the individual screening tests, the fewest proportion of subjects reported a foot exam (63.7%). Lastly, less than half of the group reported optimal screening, defined here as receiving all tests (30.6%).

Associations between risk and screening

Associations between individual risk variables and receipt of screening tests were first investigated. Among these models, looking at HbA1c, systolic blood pressure, diastolic blood pressure, and LDL independently, very few significant associations were observed (Tables 13-16). The only meaningful associations existed between LDL and dilated eye examinations, LDL (highest level only) and fasting lipid testing, and diastolic blood pressure (highest level only) and HbA1c testing. Caution must be taken when interpreting the diastolic blood pressure finding, because of the small cell size (n=4.8%).

Second, a combined model containing all of the risk variables was created and associations with receipt of screening were explored. In these models, the highest level of LDL was the only factor that was significantly associated with receipt of screening, in the presence of the other risk factors, HbA1c and systolic blood pressure. An association between LDL and fasting lipid testing and urine protein testing was observed (Table 18). The highest LDL level was positively associated with screening, compared to the lowest level of LDL risk. In the case

of fasting lipid testing, the highest level of systolic blood pressure was positively associated with screening in the combined model as well (RR=2.7, p-value=.044; 95% CI=1.03-7.3).

The combined model that contained all risk variables and screening tests was then adjusted for specialist care, gender, and health insurance and re-examined. After adjustment for these variables, the highest LDL category remained as the only risk variable associated with screening. In adjusted models, dilated eye examination joined fasting lipid testing and urine protein testing, as being significantly correlated with LDL level (Table 7). Also, the highest level of systolic blood pressure remained a significant predictor of fasting lipid testing (RR=2.8, p-value=.047; 95%CI=1.01-7.7).

9.5 Discussion

In this study, we examined the relationship between risk of developing diabetes complications and receipt of screening tests. The clinical risk factors included LDL, systolic blood pressure, diastolic blood pressure, and HbA1c and were each categorized into four-tier risk groupings for this investigation. Within this population, subjects are distributed fairly moderately at the different risk levels for the clinical risk factors. Screenings for complications in this population varied by test, but overall most patients appear to be receiving an HbA1c test and the least to receive a foot exam. We found screening associated with the highest level of LDL. However, overall, screening does not appear to be associated with clinical risk for developing complications, as almost no associations were found between other risk variables and risk levels and receipt of screening.

The study also found positive associations between high LDL levels and receipt of screening tests that include dilated eye examination, fasting lipid testing and urine protein testing. This is in-line with findings from analysis of 1991 to 2003 Behavioral Risk Factor Surveillance System (BRFSS) data. Data from this multi-year cross-sectional review of BRFSS data showed that the percentage of individuals with a history of high blood cholesterol reporting a cholesterol test is increasing.[21] The fact that we only found consistent associations between LDL risk and receipt of screening tests partially may be due to heightened awareness of coronary heart disease for diabetics among providers and patients. This increased sensitivity to coronary heart disease may translate to increased awareness of general diabetes complication risk, thus leading to higher screening rates.

There has been limited research done examining clinical risk of diabetes complications and its association with receipt of screening tests. On the other hand, there has been much more

extensive research in the area of cancer screening, as a preventive measure, and chronic disease risk factors. Classifying screening as general preventive care, our data can be compared to that found in the cancer screening literature. In the case of our data, patients at highest clinical risk levels were more likely to get screened. However in the case of cancer screening, patients with risky behavior, such as smoking, and other chronic disease risk factors were less likely to obtain breast and cervical cancer screening.[22-23] The difference in findings may be due to the fact that diabetes patients already have a diagnosed disease and tend to utilize the healthcare system on a fairly routine basis. On the other hand, cancer screening is recommended for patients who do and do not already have a cancer diagnosis. These individuals may or may not have other chronic disease. Thus, individuals in the general population without diabetes, cancer, or any other chronic disease may be healthier and may not access their healthcare system often or perceive a need for preventive care.

In this study, our goal was to explore the relationship between clinical risk for developing complications, the primary explanatory variable and receipt of screening tests. Receipt of screening tests is associated with a combination of patient, provider, and health care system factors.[24] In this report we have focused on the explanatory power of clinical risk, but these other factors play a role as well. In a limited way, we examined the role some of these factors may play on screening, via adjustment for specialist care, gender and health insurance status. Specialist care has been shown to be associated with improvements in diabetes outcomes and processes of care.[25] Additionally, males and those who are uninsured have been shown to be less likely to obtain preventive care measures, including dilated eye exams and foot examinations.[26] By adjusting for these factors, we have taken into account a few more variables that may impact

screening. However, as we only examined a limited amount of factors, it is possible that are additional variables that influence screening, that were not including in the present analysis.

There are a few additional areas of limitation associated with this study. The screening data in this study are self-reported, and thus subject to recall error. In contrast, clinical risk data was collected via clinical exam, and has a much higher degree or validity and reliability. Additionally, due to the fact that all patients are part of longitudinal cohort study, there is a potential for selection bias and their patterns of care may be affected by involvement with the study. We lost subjects from baseline due to lack of follow-up screening data. The impact is likely minimal, as there were no significant clinical risk differences between subjects with follow-up data available and those without. Likewise, the findings may also reflect a survivor bias, as many of the participants in the original EDC cohort have passed away or become to ill to participate, thus leaving the healthiest and perhaps most preventive health conscious individuals available for investigation.

In summary, we did not find many associations between risk level and receipt of screening tests. We found some associations between LDL level and screening, however by and large our data do not support the idea that screening is influenced by clinical risk for developing complications. There are two ways to interpret the lack of findings: 1) screening is valued and deemed important for all patients regardless of individual level of clinical risk, or 2) patients at highest risk for developing complications are not being targeted for secondary prevention and intervention efforts are potentially being missed. Based solely on this data, it is impossible to determine which of the above mentioned scenarios most accurately reflects the situation. This report does suggest the need for a more in-depth review of screening practices among diabetes

patients, to make sure that at minimal high risk patients are involved and targeted as a part of screening efforts.

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Table 12. Demographic Characteristics of the Study Population (N=260)

Characteristics	Number	Percent
Disease duration		
25 years or greater	170	65.4%
Gender		
Male	117	45.0%
Present smoker		
Yes	35	13.5%
Health insurance coverage		
Yes	249	95.8%
Specialist Care		
Yes	135	52.1%
Complication		
Yes	161	64.7%

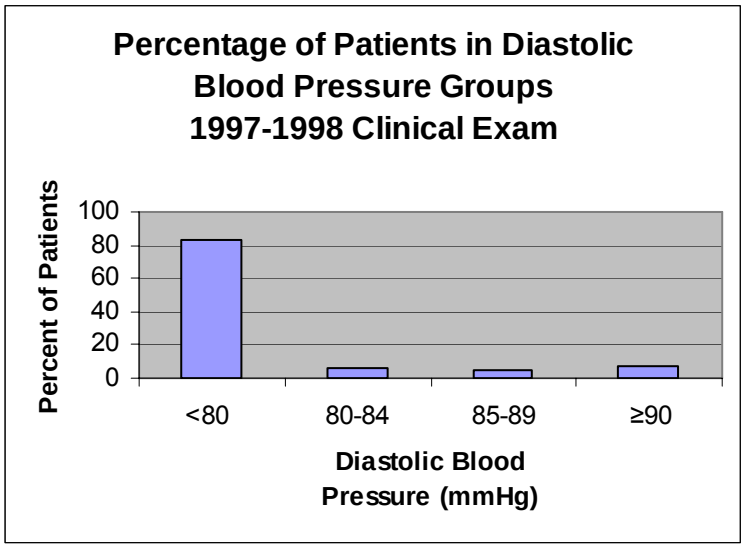

Figure 4. Percentage of Patients in Diastolic Blood Pressure Groups, 1997-1998 Clinical Exam Data

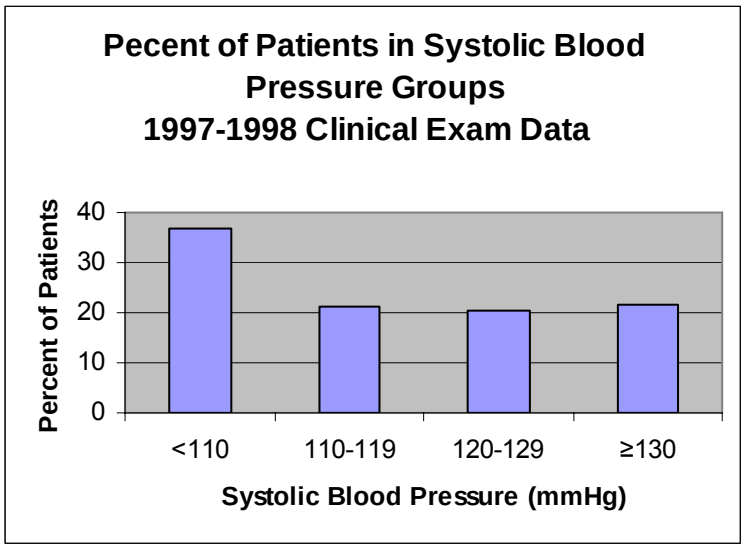

Figure 5. Percent of Patients in Systolic Blood Pressure Groups, 1997-1998 Clinical Exam Data

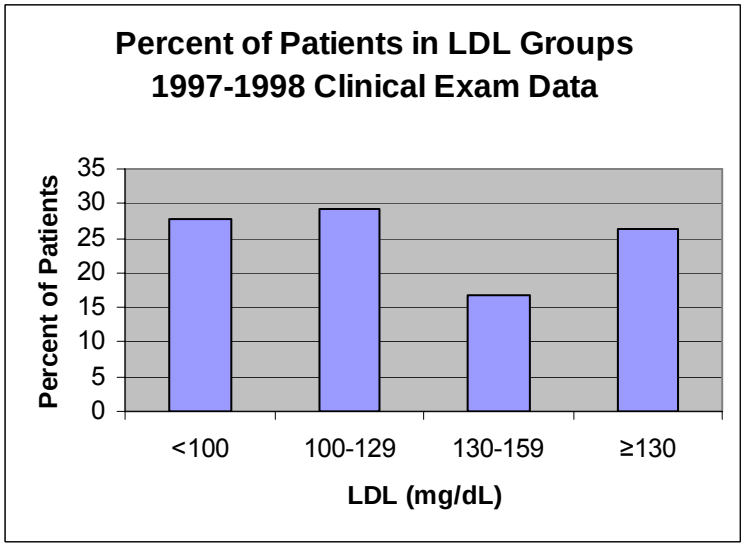

Figure 6. Percent of Patients in LDL Groups, 1997-1998 Clinical Exam Data

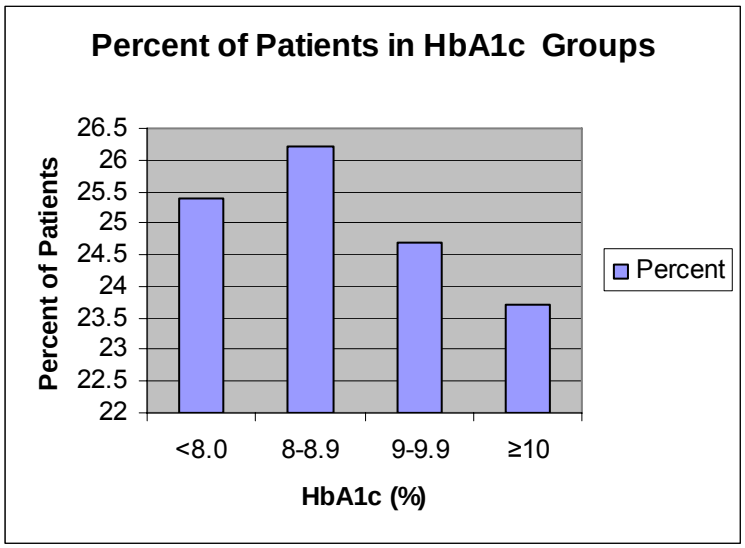

Figure 7. Percent of Patients in HbA1c Groups

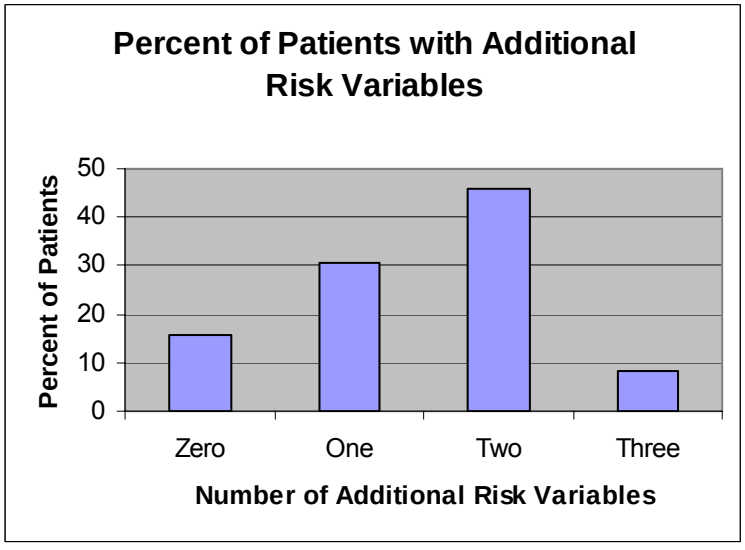

Figure 8. Percent of Patients with Additional Risk Variables

Table 13. Relative risk of receiving screening test based on level of systolic blood pressure**

Systolic Blood Pressure*	**110-119 mmHg**		**120-129 mmHg**		**≥130 mmHg**	
	RR	95% CI	RR	95% CI	RR	95% CI
HbA1c Testing	.552	.18-1.7	.633	.20-2.0	.401	.13-1.2
Fasting Lipid Testing	.96	.46-2.0	1.25	.59-2.7	1.8	.80-4.2
Dilated Eye Exam	.84	.36-2.0	1.24	.49-3.2	1.1	.42-2.7
Foot Exam	.93	.44-1.9	.72	.35-1.5	.84	.40-1.8
Urine Protein Screen	.66	.30-1.5	.48	.22-1.1	.63	.27-1.5
Optimal Screen	1.2	.54-2.5	.73	.32-1.65	1.2	.54-2.6

*Compared to less than 110 mmHg as the referent group

** Model includes additional risk factors variable (a composite variable made of any combination of at least one late stage complication, smoking behavior, and disease duration greater than 25 years)

Table 14. Relative risk of receiving screening test based on level of diastolic blood pressure**

Diastolic Blood Pressure*	**80-84 mmHg**		**85-89mmHg**		**≥90 mmHg**	
	RR	95% CI	RR	95% CI	RR	95% CI
HbA1c Testing	.60	.1-2.9	.29	.07-1.17	.18	.06-.56
Fasting Lipid Testing	1.03	.3-3.5	.30	.09-.98	1.8	.49-6.6
Dilated Eye Exam	2.9	.37-23.4	1.1	.24-5.4	.74	.23-2.4
Foot Exam	.70	.24-2.1	.75	.23-2.5	.97	.34-2.8
Urine Protein Screen	.53	.17-1.7	.53	.15-1.9	.42	.15-1.2
Optimal Screen	.55	.15-2.1	.53	.11-2.6	.91	.30-2.8

* Compared to less than 80 mmHg as the referent group

** Model includes additional risk factors variable (a composite variable made of any combination of at least one late stage complication, smoking behavior, and disease duration greater than 25 years)

Table 15. Relative risk of receiving screening test based on level of HbA1c**

HbA1c*	8-8.9%		9-9.9%		≥10%	
	RR	95% CI	RR	95% CI	RR	95% CI
HbA1c Testing	1.6	.44-6.05	.58	.19-1.74	.52	.17-1.6
Fasting Lipid Testing	1.3	.6-2.8	1.2	.55-2.6	.78	.36-1.7
Dilated Eye Exam	1.1	.43-3.02	.71	.28-1.8	.58	.23-1.5
Foot Exam	1.24	.61-2.5	1.33	.63-2.8	.93	.44-1.9
Urine Protein Screen	1.3	.57-3.1	.74	.33-1.7	.54	.24-1.2
Optimal Screen	1.3	.61-2.6	.59	.26-1.3	.702	.31-1.6

*Compared to less than 8% as the referent group

** Model includes additional risk factors variable (a composite variable made of any combination of at least one late stage complication, smoking behavior, and disease duration greater than 25 years)

Table 16. Relative risk of receiving screening test based on level of LDL**

LDL*	100-129 mg/dL		130-159 mg/dL		≥160 mg/dL	
	RR	95% CI	RR	95% CI	RR	95% CI
HbA1c Testing	3.1	1.02-9.5	1.7	.55-5.3	2.0	.71-5.5
Fasting Lipid Testing	.97	.48-2.0	1.8	.75-4.1	3.3	1.4-7.8
Dilated Eye Exam	2.2	.96-5.1	2.9	.98-8.5	2.5	1.03-6.2
Foot Exam	1.05	.52-2.1	1.2	.54-2.7	1.2	.59-2.5
Urine Protein Screen	1.7	.80-3.7	1.01	.44-2.3	2.4	1.03-5.5
Optimal Screen	1.1	.51-2.4	1.1	.46-2.8	1.7	.77-3.7

* Compared to less than 100 mg/dL as the referent group

** Model includes additional risk factors variable (a composite variable made of any combination of at least one late stage complication, smoking behavior, and disease duration greater than 25 years)

Table 17. Risk estimates for highest LDL grouping compared to lowest LDL level, adjusted for other risk variables in combined model*

Characteristic	Relative Risk	P-value	95% CI
HbA1c Testing	2.1	.20	.69-6.3
Fasting Lipid Test	3.6	.006	1.5-8.8
Foot Exam	1.2	.59	.57-2.6
Dilated Eye Exam	2.6	.053	.99-6.6
Urine Protein Exam	2.5	.043	1.02-6.03
Optimal Screening	1.6	.28	.68-3.6

*Other variables in model include HbA1c, SBP and the additional factor composite score variable

Table 18. Risk estimates for highest LDL grouping compared to lowest LDL level, adjusted for other risk variables in combined model, specialist care, gender and health insurance*

Characteristic	Relative Risk	P-value	95% CI
HbA1c Testing	2.7	.12	.77-9.6
Fasting Lipid Test	3.5	.007	1.4-8.9
Foot Exam	1.3	.52	.60-2.8
Dilated Eye Exam	2.8	.042	1.04-7.4
Urine Protein Exam	2.7	.04	1.05-7.1
Optimal Screening	1.8	.19	.75-4.4

*Other variables in model include HbA1c, SBP and the additional factors

10.0 Discussion

Diabetes mellitus, a chronic disease affecting many individuals in the United States, has increased over the past decade, a trend that is expected to continue (Centers for Disease Control and Prevention 2003; Engelgau et al. 2004). Diabetes is a significant public health issue with many types of adverse outcomes and disability. The overwhelming majority of diabetes morbidity and mortality is associated with chronic complications, including retinopathy, nephropathy, neuropathy, peripheral vascular disease and coronary heart disease (Centers for Disease Control and Prevention 2004b). The main precursors of these conditions are poor control of blood glucose, blood pressure and lipid control. The impact of these conditions can be moderated through appropriate screening and treatment. Screening tests recommended by national panels include an annual fasting lipid test, urine protein test, dilated eye examination, foot examination, and quarterly HbA1c and blood pressure testing at each physician office visit (American Diabetes Association 2005). Despite the value of screening, little is yet known about screening practices among persons with type 1 diabetes. To date, the literature on screening has focused on persons with type 2 diabetes and few reports have identified correlates and factors related to the optimal use of screening. As this group of patients represent younger individuals in the productive phase of their lives, research focused on screening in this population is especially important.

10.1 Summary of Findings

This dissertation examined screening for diabetes complications in a cohort of type 1 diabetes patients. The aims were to: 1) identify the frequency and trends in screening; 2) identify general correlates of screening as well as to evaluate the influence of patient behavior and health care access factors on receipt of screening tests and examine the association between clinical risk

of developing complications and receipt of screening tests to detect complications. The findings in this report reflect some of the first comprehensive screening data focused exclusively on type 1 diabetes patients.

In the first aim, the frequency and trends in screening in a population to type 1 diabetes patients was described. Most, but not all patients received at least one of the recommended screening tests, as prescribed by the American Diabetes Association (N=88%). Although the prevalence of screening for individual tests in this cohort was comparable to that described in the literature, the level of optimal screening was low (N=38%) (Glasgow & Strycker 2000). While the definitions of optimal screening have varied among published studies, the levels have all been low, which is in unison with our findings (Ahluwalia et al. 2000; Beckles et al. 1998). Trends in screening prevalence over time were evaluated. By analyzing screening data at three time points, we found that screening rates are improving. This finding is also in line with data presented in the literature that suggests screening is becoming more common.

In specific aim two, correlates of screening were investigated. When investigating general factors related to screening, use of specialist care, female gender, and patient mediated glycemic control were found to be positively correlated with receipt of screening tests. Specialist care and gender and to a lesser extent patient self-management, have been shown in the literature to be associated with better diabetes preventive care (Hjelm et al. 2002; Zgibor et al. 2000). Our findings in type 1 diabetes are similar to those found in the literature focused primarily on type 2 diabetes subjects.

The influence of patient behavior and health care access factors on the receipt of screening tests was also examined in aim two. The patient behavior of daily blood sugar testing and the access factors of specialist care, intensive insulin therapy, and the number of physician

visits was found to be positively associated with receipt of screening tests, at three different time points. Within this cohort, access level factors appear to have a stronger influence on screening than do patient self-management behaviors. The literature highlights the need for a multi-faceted diabetes management programs that incorporate patient and access factors; our data support this, but favor emphasizing access factors more heavily to improve screening. This study also explored which patients and access factors are improving over time. The findings of this study indicate that many patient self-care factors are improving over time, while most access factors have remained fairly constant. Data from national population based samples support the findings of improvements in patient self-management behavior (Petitti et al. 2000).

The association between clinical risk for developing complications and receipt of screening tests to detect complications was also investigated. The basis of the risk estimation was control of blood glucose, pressure and lipids; all of which have been shown to be associated with developing each of the chronic complications. In this study, risk was not associated with receipt of screening tests for almost all levels of glycemic, blood pressure and lipid control. There were a few associations observed between the highest levels of clinical lipid risk. To the knowledge of the investigators, this is one of the first studies to examine this association in diabetes secondary prevention; however the cancer literature has found associations between risk behavior and cancer screening (Rakowski et al. 1999).

In summary, the issue of screening for chronic diabetes complications in type 1 diabetes was explored. The general prevalence of screening, trends in screening rates, have been described and correlates of screening have been identified. The findings of this report are significant and have implications for diabetes preventive care.

Overall, the findings show screening rates for individual tests are fairly high, and have improved over time. This is a good indicator that diabetes care is improving, and that evidence-based guidelines that included routine screening for diabetes complications are being adopted. However, the rates for receiving all tests, which we define as optimal screening, were considerably lower. Rates for individual tests are more than double the rates for optimal screening, which implies there may be a disconnect in obtaining complete screening. Thus, this work suggests that emphasis should be placed upon comprehensive care of diabetes patients, which involves receiving all recommended screening tests. While there may be room for modest improvements in screening rates for individual tests in order to bring rates even closer to 100%, focusing on increasing optimal screening may have the largest impact on diabetes preventive care.

In addition to describing screening prevalence, it was shown that use of specialist care, female gender, and better patient self-care were associated with more screening. The investigation found that compared with patient-level factors, access level factors, that included intensive insulin therapy and number of physician visits in addition to specialist care, have stronger influence on screening practices. These findings give direction for the planning and implementation of interventions and policies to improve screening, and in particular optimal screening, as these data have shown these rates to be the from the ideal. Access factors have the greatest impact on screening, and efforts aimed to increase optimal screening that incorporate these factors may be most successful and improve diabetes preventive care.

Lastly, along with describing the prevalence and correlates of screening, the association between clinical risk of developing complications and receipt of screening tests was examined. Overall, patients at highest clinical risk were getting screened at the same levels as patients with

average risk, for both individual tests and optimal level screening. Clinical risk factors should be and indicator for targeted screening efforts, as patients in poor lipid, glycemic, and blood pressure control are more likely to develop complications. The lack of an observed association between clinical risk and screening for chronic complications highlights a potential area for improvement. In addition, optimal screening is especially important in this group of diabetes patients, as all of the chronic conditions have overlapping clinical risk factors, which makes screening for all complications of particular value for these patients. Addressing access factors, such as provider education or the implementation of a system that would flag diabetes patients at high clinical risk for developing complications, may help to ensure that this group of patients gets the necessary diabetes preventive care, which includes optimal screening.

This research has successfully identified the prevalence of screening and factors associated with screening. The findings indicate that the areas in need of improvements include optimal screening rates and targeting screening endeavors towards patients at clinical risk for developing complications. These data suggest that creating interventions that incorporate access factors may be the most fruitful strategies to improve screening rates. Thus, incorporating all of these findings into interventions and health care policy may make the greatest impact on screening and diabetes preventive care among type 1 diabetes patients

10.2 Applications to disease management

Diabetes management incorporates a coordination of actions from the patient, provider, and health care system. Disease management involves an organized and integrated approach to health maintenance that emphasizes patient and provider knowledge, behaviors and the structure and resources of health care systems (Norris et al. 2002). A key component of proper diabetes management is to ensure that patients are treated according to evidence-based practice guidelines

and that there is process and outcome measurement, evaluation, and management. A critical function of diabetes disease management is the prevention of chronic complications, which is accomplished via early detection.

This research examined the screening issue in type 1 diabetes, and the coordination of patient, provider, and health care systems is necessary for screening at the recommended level to occur. In this investigation, many variables that fall under these disease management headings and their relationship to receipt of screening tests was analyzed. At the patient level, glycemic control and gender was associated with screening. At the provider level specialty care, intensive insulin therapy, and the number of doctor visits was correlated with screening. We examined the potential affect of health care system factors, such as inadequate insurance and barriers to seeing a physician, but no significant associations were uncovered.

All data are from the patient-perspective, which limits the conclusions that can be drawn from our findings. Also, the variables available for analysis were somewhat sparse, which hindered how in depth our analysis could go, with regards to complete disease management. Truly comprehensive information regarding complete disease management would require individual investigation of patients, providers, and health care systems and their impact on screening. There is also overlap between all of these factors and it was not possible for us to isolate variables completely as a patient, provider, or health care system factor. For instance, it is possible that patient motivation and behaviors influences their health care utilization, thus prompting them to visit a specialist. Another scenario could be that specialists have trained to particularly treat diabetes patients, have high number of diabetes patients as clients, and thus make it a point to stay abreast of evidence-based guidelines and act accordingly; which brings them to order screening tests independent of patient behavior. It is also possible that specialists

encourage patients to be more pro-active and involved in their health care, which may influence screening as well.

These findings have produced valuable information that can be used to bolster diabetes management and may help explain the specific areas of the broad disease management components, patient, provider and health care systems inputs, that impact screening for diabetes complications in type 1 diabetes. There have been several areas identified that warrant further exploration as potential intervention areas to improve screening rates.

10.3 Limitations

This research is associated with several limitations that must be considered when interpreting our findings. First, with the exception of clinical exam data, all data are self-reported, which could result in a recall error. Validation studies surrounding self-report of diabetes preventive care service, found that patients tend to over-report use of screening tests for complications (Fowles et al. 1999). Thus, it is possible for the reported screening rates in this study to be higher than what they actually are.

Second, the findings from two manuscripts of this thesis came from a cross-sectional design. The main limitation with this study design is the inability to determine temporality in observed relationships. However in this research several time points were investigated cross-sectionally and there were similar results at each time point, which supports these findings. Although causation was impossible to determine, valuable prevalence estimates of screening in the type 1 diabetes population and some insight into predictors of screening in these patients have been provided. A strong foundation to develop hypotheses to design and implement prospective studies has also been provided.

There are limitations associated with the study population. The subjects for this study are all a part of the Pittsburgh Epidemiology of Diabetes Complications cohort, and all patients live within 100 miles of Pittsburgh. Thus, despite the fact this cohort is epidemiologically representative, it may not be representative of the general type 1 diabetes population. Additionally, the study subjects in this cohort were diagnosed between 1950 and 1980 and at the time of analysis the mean disease duration was 28 years, thus representing older type 1 diabetes patients. Therefore, these findings may not be generalizable to younger type 1 diabetes patients.

Additionally, because we have used patients involved in a cohort study, a selection bias may also be observed. Health care practices for study participants may differ from type 1 diabetes patients who are not a part of the study, and involvement in the study may influence health care practices. The reported data may also reflect a survivor bias inherent to this cohort. The original study consisted of 658 type 1 diabetes patients, however our analysis reflect data from roughly half of the original cohort. Members of the original cohort may have passed away or become too sick to participate. Individuals that have remained in the study may have better disease management, which includes higher screening rates and higher rates glycemic control and other self-care behavior, than those who no are no longer involved in the study.

10.4 Public Health Significance of Research

The findings from the research have major public health implications. The majority of diabetes disease burden comes from chronic diabetes complications. These conditions, which are associated with substantial morbidity and mortality and subsequent high health expenditures, are a serious concern among type 1 diabetes patients. Type 1 diabetes patients are a special group: they are diagnosed with diabetes at a young age and need to and are expected to be a part of the workforce. Data from this research have given more insight into the issue of screening in type 1

diabetes, and the findings can be used to improve screening rates in type 1 diabetes community. These results can be used to design interventions and policies to bolster preventive care, thus reducing rates of late-stage retinopathy, nephropathy, neuropathy, peripheral vascular disease, and coronary heart disease.

The main benefit of this research is the potential it has to improve diabetes outcomes by reducing morbidity and mortality associated with chronic conditions. Subsequently, there would be advancements at both the diabetic patient and societal level. By diminishing chronic disease rates, there would be a reduction in hospitalizations and costs for treatments and other health care for diabetes patients. Currently, diabetes patients spend a substantially higher amount of money on health care than do non-diabetes patients (Aro et al. 1994; Laditka et al. 2001). Reduction in health care expenditures related to complications would lessen the disparity in health care costs between diabetes patients and the non-diabetic general population. Diabetes patients would also have greater fiscal stability resulting from lower rates of work absenteeism due to chronic disease. The United States economy would also benefit, because there would be a healthier workforce, as work days lost due to complications would be lessened. In addition, the amount of federal dollars used to treat late-stage complications would be reduced. Overall, quality of life for diabetes patients would improve if screening rates increased and disease rates for chronic complications were lowered.

10.5 Future Research

This research was the first step in investigating the issue of comprehensive screening in type 1 diabetes. The findings provide data that can be used immediately to describe screening in type 1 diabetes, which has not been done well previously, and it also lays a foundation for the next wave of research to be conducted in this area.

This research has consistently shown specialist care to be associated with screening. More research now needs to be conducted that focuses specifically on patients not enrolled in specialty care. Many diabetes patients do not see specialists, thus it is important to target research that addresses this group of patients. More information on the characteristics of patients and screening patterns of those who only visit primary care physicians is needed. There is also a need for more information on primary care physicians who see diabetes patients, with respect to referral rates for screening tests, the percentage of their patients receiving recommended screening, and characteristics of providers with patients largely on target. Practice redesign to improve treatment of diabetes patients with respect to secondary prevention in primary care may improve screening rates. Another approach could be to use this information to design interventions to get patients to receive specialty care at a higher rate. Educating patients about the benefits of seeing a specialist may increase the number of patients receiving specialty care, thus leading to higher rates of screening for chronic complications. Informing health insurers of the potential reduction in health care costs from screening associated with screening may persuade these payers to encourage patients to see specialists and reduce obstacles, such as referrals, limited selection of available provider, and high co-payments for office visits, to do so.

Another finding of this research is that patient self-care is positively associated with screening for diabetes complications. Although physicians order screening tests, we found there is also a patient-level component that impacts screening. It is likely that patient attributes such as self-efficacy contribute to self-care behavior, and rather these specific attributes are responsible for improvements in screening. Therefore, further investigation between the relationship of patient behavioral characteristics and screening is needed.

Along with specialty care and patient self-care, this investigation found that women were more likely to obtain screening tests. In general, the health literature has shown that men tend to have poorer preventive care practices and lower utilization of the health care system than women. Diabetes management is critical and merely highlighting the differences in screening and other health care practices between genders is not sufficient. A large population based study examining reasons for observed differences in diabetes preventive care between men and women is warranted. Likewise, as our findings reflect those of a type 1 diabetes cohort, this next study should focus exclusively on type 1 diabetes patients or at least oversample them.

Finally, health care access factors such as intensive insulin therapy, and the number of doctor visits were found to be associated with screening. Interventions targeted at providers to encourage them to consider intensive insulin therapy for their type 1 diabetes patients, as well as interventions designed to help them encourage patients to be more involved in their diabetes care related to chronic disease management may increase diabetes preventive care. Leading patients towards regular visits with their health care provider and being compliant with intensive insulin therapy recommendations has the potential to ultimately improve screening rates. Health insurance groups may also facilitate this by removing barriers such as high co-pays for medications and office visits and limited provider selection.

10.6 Implications for Health Policy

Screening for chronic complications has been proven to be an effective means to prevent or delay the progression of diabetes-related chronic conditions. Additionally, screening is a part of evidence-based guidelines currently in place to ensure the best possible diabetes care. The American Diabetes Association recommends diabetes patients receive routine screening tests to detect early forms of retinopathy, nephropathy, neuropathy, and cardiovascular disease

(American Diabetes Association 2005). Screening is deemed so valuable, it is has been incorporated into the National Diabetes Agenda, where the goal is to increase screening rates for dilated eye exams, foot exams and HbA1c testing. Along those lines, many health maintenance organizations also promote screening among enrolled diabetes patients and have established programs to facilitate this behavior. The findings from this study can be used to help the adoption of screening at the recommended levels and support existing policies that encourage screening behavior. This research has identified deficits in optimal screening rates and screening amongst diabetes patients at high risk for developing complications, which are areas where interventions or modifications to current policies that incorporate these specific items as target areas may be beneficial. Information on correlates of screening that can be used to develop programs to improve screening rates and maintain current policy has also been provided.

10.7 Conclusion

In this research, screening for chronic complications in a cohort of type 1 diabetes patients was examined. The prevalence of screening is improving over time; however few patients still receive all recommended tests. Many variables associated with screening were also identified, specifically with specialty care and self-monitoring of blood glucose levels to be strongly correlated with screening. Thus this research has highlighted deficits in screening practices and areas that may be targeted to improve screening. Diabetes complications are perhaps the most burdensome disease outcome, making early detection of these conditions extremely worthwhile. If properly utilized, screening has the potential to reduce rates of diabetes complications and improve quality of life in diabetes patients.

APPENDIX

Review of the Screening Literature

Table A1. Review of Screening Rates for Diabetes Complication Reported in the Literature*									
Primary Author	**Study Population/Data Source**	**Methods**	**Type of Diabetes**		**Dilated Eye Exam**	**Foot Exam**	**HbA1c**	**Urine Protein**	**Lipids**
			Type 1	**Type 2**					
Payne S, 1999	CaliforniaCare diabetic enrollees, N=3,612; 1997	Medical record review	NS	NS	77.90%	65.20%	89.00%	TNR	TNR
Saaddine, 2002	Third National Health and Nutrition Survey (NHANES III) (1988-1994); Behavioral Risk Factor Surveillance System (BRFSS) (1995);	Self-report	NS	NS	63.3%; Insulin users: 72.2%	54.8%; Insulin users: 67.3%	28.80%	TNR	85.3%†; Insulin users 86.4%
Ahluwalia, 2000	Noninstitutionalized adults (age ≥18 years) in Kansas contacted by the Kansas Department of Health and Environment	Self-report	7.70%	87.8%; 4.5% NS	64.50%	27.2%‡	TNR	TNR	TNR
Beckles, 1998	1994 BRFSS data from 22 states that	Self-report	7%	88%; 5%NS	Type 1-74.9%	Type 1-63.6%	Type 1-78.6%	TNR	TNR

Table A1 (Continued)	used the diabetes module								
Peters, 1996	353 Patients enrolled in a large HMO in California between Jan 1993-Jan1994.	Medical record review	8.50%	78%	TNR	6%	44%	48%	56% total cholesterol; 50% triglycerides
Harris M, 2000	Third National Health and Nutrition Survey (NHANES III) (1991-1994)	Self-report		100%	52.10%	TNR	TNR	TNR	87%**
Clark C, 2001	MCO in Las Vegas, Nevada; N=370	Medical record review	NS	NS	53.90%	0%	TNR	17%	66%
Petitti, 2000	Kaiser Permanente Health Plan Medical Group-Patients enrolled January 1, 1994-December 31, 19997	Medical record review/Administrative databases	NS	NS	TNR	TNR	1994:60% 1995:57% 1996:61% 1997:64%	1994:10% 1995:13% 1996:20% 1997:33%	1994:36% 1995:35% 1996:38% 1997:42%
Ozminkowski, 2000	18,403 patients enrolled in 35 health plans across the U.S. in 1996	Medical record review	NS	NS	29%	TNR	20%±	38%	43% total cholesterol; 15% triglyceride; 31% HDL

Table A1 (Continued)									
Sikka, 1999	Members of HMO recruited from two largest clinics within the Jacksonville Health Care Group; N=133	Medical record review	10.50%	88%; 1.5%NS	TNR	TNR	TNR	77%	TNR
Weiner, 1995	Medicare patients from Alabama, Iowa, and Maryland (N=2980) between July 1990-June 1991 (patients aged 65 years or older)	Administrative databases/Claim forms	NS	NS	45.90%	TNR	16.30%	TNR	55.10%
Streja, 1999	Chart audit of 22 primary care providers of an HMO; 1993-1994	Data obtained from chart audit or administrative data from the medical group.	NS	NS	62%†	TNR	TNR	80%†	78%†

Table A1 (Continued)									
Engelgau, 1998	Three MCO, 1993 data, N=16,363	Electronic medical review, Analyzed seperately by MCO	NS	NS	23.2%-46.0%; Insulin users: 34.6%-54.1%	TNR	34.3%-81.0%; Insulin users:38.9%-80.3%	micro urine- 0-.5%; macro urine-34.3-81.0%; Insulin Users: micro-0-.9%,macro-43.7%-57%	TNR
Schoenfield, 2001	Diabetic residents of Suffolk County, New York, between October 1993 and May 1995	Self-report	15%	85%	65%	TNR	TNR	TNR	TNR
Centers for Disease Control, 2001	BRFSS data from 1995 and 2001 from 35 states	Self-report	NS	NS	1995: 58.9%; 2001: 65.9%	1995: 56.0%; 2001: 62.3%	TNR	TNR	TNR
Centers for Disease Control, 2005	BRFSS data from 2002 from 45 states	Self-report	NS	NS	69.70%	38.20%	71.2%±	TNR	TNR
Kerr, 2004	Five VA Medical Centers and Eight Commerical Managed Care	Medical chart review and patient survey	NS	NS	VA-57%; CMC-28%	VA-87%; CMC-50%	VA-93%; CMC-83%	VA-92%; CMC-81%	VA-79%; CMC-63%

Table A1 (Continued)	Groups								
Miller, 2000	Patients with 2 or more visits to Endocrinology Clinic in 1998	Medical chart review	20%	80%	74%	87%	TNR	55%	70%
Martin, 1995	Kaiser Permanente Medical Care Program, Oakland. Patients drawn from pharmacy data between January 1 and June 30, 1992; N=378	Medical charts were reviewed from March 1992-June 1993. Groups were analyzed by race: African-American, Hispanic, White, Other	NS	NS	66.7%-82.8%†	55.6%-62.1%±†	41.4%-51.9%±†	4.1%-37.5%±†	51.9%-58.6%†

Legend: * = All rates reported are annual rates unless otherwise noted; NS= Not specified; TNR=Test not reported; † = biannual; ± = at least two tests; ‡ Tests reported in ADA compliance, referring to four or more foot exams for insulin users and two for nonusers

Table A2. Correlates of Complication Screening Reported in the Literature					
Primary Author	**Study Population/Data Source**	**Screening tests**	**DM Type**	**Methods**	**Results**
Payne S, 1999	CaliforniaCare diabetic enrollees, N=3,612; 1997	Dilated eye exam (annual); Foot exam (annual); HbA1c test (within past 12 months)		Medical record review	Correlates of retinal screening: age (OR 1.1, p<.001), English primary language (OR 1.32m p<.03), seeing dietician (OR=1.48, p<.001), diabetes educ class (OR=1.94, p=.001), SMBG more than once per day (OR=1.72, p<.001) and moderate or high prescription drug use (OR=1.1, p<.0001); Correlates of annual foot examination: age, male gender, english as primary language, specialist care, seeing dietician, insulin use, combined insulin/oral med use, daily SMBG; Correlates of HbA1c test

Table A2 (Continued)					within the past 12 months: dietician, high use of prescription drugs, diabetes support group, spanish as primary language
Saaddine	Third National Health and Nutrition Survey (NHANES III) (1988-1994); Behavioral Risk Factor Surveillance System (BRFSS) (1995);	Cholesterol monitoring (biannual), Foot exam (annual), Dilated eye exam (annual), HbA1c test (annual)	Not specified, but have insulin use and length of insulin use; 21.8% in NHANES III used insulin for at least 15 years and 30.6% of BRFSS used insulin for at least 15 years	Self-report	After controlling for age, sex, ethnicity, education, health insurance, insulin use and disease duration: insured persons were more likely to have an annual dilated eye exam (66.5% vs. 43.2%; p=.001). persons who used insulin were more likely to report annual dilated eye exam (72.2% vs. 57.6%; p=.001) and foot exam (67.3% vs. 47.1%, p=.001) compared to nonusers. persons 65-75 were more likely than persons 18-44 years to have biannual lipid testing (90.4% vs. 53.4%; p=.001) and annual eye exam (69.7% vs. 53.4%, p=.003)

Table A2 (Continued) Ahluwalia, 2000	Adults (age ≥18 years) in Kansas contacted by the Kansas Department of Health and Environment for a phene survey (noninstitionalized)	Foot exam (four or more for insulin users and 2 or more for nonusers), blood pressure measurement within past 6 months, dilated eye exam within the past year	Type 1 - 7.7% Type 2 - 87.8% Not classified- 4.5%	Self-report	In bivariate analyses, having a regular HCP, having a health care provider who scheduled the follow-up appointment, being a former smoker, being physically active, and being male were associated with receipt of recommended care. In adjusted models, males (OR 1.6, 95% CI 1.1-2.5), those who had HCP scheduled follow-up vists (OR=2.7, 95% CI=1.6-4.8) and former smokers compared to current smokers (OR=3.1, 95%CI=1.6-6.9)
Beckles, 1998	1994 BRFSS data from 22 states that used the diabetes module	Dilated eye exam (annual); Foot exam (annual); at least one HbA1c	7% Type 1 88% Type 2 (of this 34% reported current insulin use) 5% could not be classified.	Self-report	Among insulin users[with all models adjusted for age,race,education,health insurance]: individuals with less than high school education were more likely to have their feet inspected compared to those with greater than hs (OR=.46, 95%CI=.24-.87) and those with health insurance were more likely to have a foot exam (OR=4.3, 95%CI=1.36-12.51) abd dilated eye exam than those with no insurance (OR=3.23, 95% CI=1.32-7.9). Only 1% of noninsulin users and 3% of insulin users met all five ADA standards (for insulin users defined as SMBG at three times per day (1 for nonusers), 4 or

Table A2 (Continued)					more HCP visits per year for insulin users (2 for nonusers), awareness of HbA1c, annual foot exam, annual dilated eye exam)
Weiner, 1995	Medicare patients from Alabama, Iowa, and Maryland (N=2980) [100% sample] between July 1990-June 1991 (patients aged 65 years or older)	HbA1c, ophthalmologist examination, cholesterol, all over 12 month period	Not Specified	Administrative databases/Claim forms	Patients of general practitioners less likely to meet standards of recommended care than patients of internists or family practitioners.
Schoenfield, 2001	Diabetic residents of Suffolk County, New York, between October 1993 and May 1995; recruited via a multimedia community-wide campaign	Dilated eye exam (annual)	Type 1-15% Type 2-85%	Self-report	Subjects not receiving a dilated eye exam in the previous year were more likely to be male (52% vs. 44%, p,.001), younger (p,.001) and less likely to have insurance coverage (87% vs. 96%, p,.001)

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