PREVALENCE, INCIDENCE AND RISK FACTORS OF ERECTILE DYSFUNCTION IN MALES WITH TYPE 1 DIABETES ENROLLED IN THE PITTSBURGH EPIDEMIOLOGY OF DIABETES COMPLICATIONS STUDY (EDC) (1986-2007)

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Objective: To: 1)determine the prevalence and incidence of ED in males with T1D enrolled in the Pittsburgh Epidemiology of Diabetes Complication (EDC) study from 1986 to 2007; 2)identify risk factors for development of ED; 3)identify the development of ED in relation to other markers of neuropathy; and, 4) determine behavioral and cognitive risk factors associated with the development of ED.

Design: The EDC was a cohort study of 333 males with T1D: mean age of 27.53years (SD±7.8, range 8.5-47.4); 331 Caucasians and 2 African Americans; and, duration of diabetes of 19.6years (SD±7.5, range 7.7-37.4). Age-specific ED prevalence was determined from baseline (1986-1988) while age-specific incidence was determined from longitudinal data (1988-2007).

Results: *Prevalence rate* was 10.4 %. Thirty-one had ED: mean age of 35.8years (SD±5.3, range 22.9-44.8) and mean duration of diabetes 26.9years (SD±5.9, range 8.1-37.4). Males with prevalent ED did not statistically differ from males without ED in metabolic control (HbA1), education, income, or the current use of ACE or lipid lowering medications. Associated risk factors for the 31 prevalent cases included; CDSP, HDL and BDI score. *Incidence rate* was 17.78 % (n=54) from 1989-2007 with a mean age of 40.61years (SD±5.9, range 26.7-60.8) and

mean duration of diabetes of 32.54years (SD±5.88, range 20.9-51-9). Mean HbA1 was 10.68% (SD±2.19). Associated risk factors for the 54 incident cases included; CDSP, nonHDL cholesterol, and BDI score. E/I Ratio was significant ($p<.01$) at the time of the event, but not in the preceding event cycle ($p=.18$). CDSP was significant ($p<.01$) in the preceding cycle to ED development and at the time of event ($p<.01$). For the repeated measure analysis, CDSP was significant in the preceding cycle to the ED development but not at the time of the event. The following differences were found between those with and without ED: knowledge of diabetes ($p=.04$); self-management ($p=.10$); and, perception of severity ($p=.08$). However no significant difference was found between the two groups for self-efficacy.

CONCLUSION: CDSP, HDL, nonHDL and total BDI score were risk factors for development of ED in males with T1D. Therefore, these should be assessed for frequently in males with T1D.

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PREFACE

This dissertation is dedicated to my parents who, when I was a child, encouraged me to have such heroes as Annie Oakley and Peter Pan, to fulfill my dreams and to work to my potential. Additionally this is dedicated to my family who provided continued support after my decision to return to an academic environment.

Acknowledgement and much appreciation are given to my esteemed Dissertation Committee, Chair, Dr. Denise Charron-Prochownik, Co-Chair, Dr. Trevor Orchard, and Drs. Jan Dorman and Susan Sereika, for their continued support and guidance throughout this academic endeavor. The recognition of their professional knowledge, generosity, unrelenting time and friendship is greatly appreciated. Thank you!

1.0 INTRODUCTION

The focus of this dissertation is erectile dysfunction (ED) in males with Type 1 Diabetes (T1D) enrolled in the Pittsburgh-Epidemiology of Diabetes Complications Study (EDC) (1986-2007). This chapter provides a brief introduction to erectile dysfunction (ED) in males with T1D, the problem statement and purpose of this research, as well as the specific aims and research questions followed by the significance of this study.

Expanding a previous definition of sexual dysfunction that only included impotence, the National Institutes of Health Consensus Conference, in 1993, defined the complication of erectile dysfunction (ED) as an inability *to achieve and maintain an erection sufficient for satisfactory sexual performance to include libidinal, orgasmic and ejaculatory dysfunctions* (Conference, 1993). Worldwide estimates of ED are approximately 150 million men. Within the United States alone, it is estimated that approximately 30 million males are affected with erectile dysfunction (MacDonagh, Ewings, & Porter, 2002; A. D. Seftel, Sun, & Swindle, 2004). In a retrospective cohort study of a representative national managed care database including 51 commercial health plans and 28 million members in the United States, Sun et al (Sun, 2006) found 285,436 males reported an ED diagnosis from 1995-2001. Table 1.1 depicts the diagnosis of ED by percentage of claims filed, reported by region within the United States.

Table 1.1. Percentages of Claims Reporting ED Diagnosis by Region within the US (1995-2001)

Region	% Reporting ED	Population
East	21.96%	n=62,694
South	32.78%	n=93,560
Midwest	33.95%	n=96,902
West	11.13%	n=32,280

The mean **age** of males with ED was found to be 8.1 to 12.3 years older than the mean age of males without ED. Of the males reporting ED, 87% were between the ages of 36 and 65 years of age (See Table 1.2). The actual **prevalence** of ED is probably somewhat higher than reported by Sun et al (Sun, 2006) in this review. Males with Medicaid, Medicare or non-managed insurance plans were not part of this claims database review and only those males with ED who sought care for ED were included for analysis, therefore, actual prevalence rates of ED are suspected to be somewhat higher.

Table 1.2 Age Distribution of Males with ED (bolded area represent 87% of Males between 36-65 Years of age)

Age Groups (Years)	% of Cohort Reporting ED
18-25	0.8
26-35	4.9
36-45	**16.1**
46-55	**35.7**
56-65	**35.3**
66-75	5.2
76-85	1.9
86+	0.2

ED significantly affects males with co-morbidities. Approximately 42% of males with **hypertension**, 42% for **hyperlipidemia**, 20% with **diabetes**, 11% with **depression**, 24% for hypertension and hyperlipidemia, and 13% for hypertension and diabetes mellitus, also have ED (A. D. Seftel et al., 2004).

ED is a well documented and prevalent complication of type 1 and 2 diabetes. It is estimated that approximately 50-70% of all males with type 1 diabetes (T1D) will develop a functional sexual disorder within 10 years of their initial diabetes diagnosis. For males with Type 2 Diabetes (T2D), ED will develop in approximately 46% of those males (Vickers, 2002).

The prevalence of ED will increase as the proportion of diabetes cases continues to escalate. It is predicted that in the year 2025, the countries with the most number of diabetes cases will be India, China, and the United States (King, 1998) and in the year 2050 there will be 48.3 million people in the United States alone with diabetes (Venkat Narayan, Boyle, Geiss, Saaddine, & Thompson, 2006). Diabetes is a major health burden for American males. In 2005, it was estimated that approximately 20.8 million people or 7.0% of the U.S. population had type 1 and 2 diabetes (www.diabetes.org/diabetes-statistics, 2/18/2007). There are 10.9 million men within the United States with diabetes (www.diabetes.org/diabetes-statistics, 2/18/2007).

TID, previously known as juvenile onset diabetes or insulin dependent diabetes mellitus (IDDM), is a major chronic disease causing significant public health problems. T1D is commonly diagnosed during childhood and early adolescence, though can be diagnosed at any age. T1D is seen in about one in every 400 to 600 children and adolescents. Data from the Allegheny County Registry, Pennsylvania, showed a rather rapid increase in **incidence** for the period 1985-1989, within the total observed period 1966 to 1989. This reflects an 83% increase in incidence. Most rapid increase in incidence was noted in the 0-4 year age group and non-white males. Also contributing to the increase was a higher incidence of diabetes for the African-American group noted as 17.6/100,000. This is higher than the incidence for Caucasians, which was noted as 16.5/100,000. A threefold higher incidence of diabetes among the African-American group, ages 15-19 years, was 30.7/100,000 as compared to the Caucasian group of 11.2/100,000. The 1990-1994 incidence rates for Allegheny County for the African-American group were two and three times higher than the incidence reported for this group in the years 1985-1989 and 1980-1984 respectively (IM Libman & LaPorte, 2005).

Diabetes can cause short and long term complications. Long term complications account for over 200,000 deaths per year (www.diabetes.org/diabetes-statistics, 2007). The increase in morbidity and mortality is due to chronic conditions resulting from retinopathy, nephropathy, neuropathy and cardiovascular system involvement.

ED is a form of **autonomic neuropathy (AN)** . ED may be considered an important precursor in the development of cardiac and vascular disease. Males with ED and T1D have an increase in the severity of coronary heart disease as well (A Vinik, Maser, Mitchell, & Freeman, 2003).

The American Diabetes Association cites the importance of early recognition and appropriate management of neuropathies (Boulton et al., 2005). Diabetic autonomic neuropathy (DAN) can potentially affect every system within the body and cause an increase in morbidity and mortality in those with T1D (Maser, Pfeifer, Dorman, Becker, & Orchard 1990; A Vinik et al., 2003). Approximately 20% of those with diabetes will have **cardiovascular autonomic neuropathy (CAN)** (A Vinik et al., 2003). In a 1990 study by Orchard and Maser (Maser et al., 1990),168 people with insulin dependent diabetes, between 25-34 years of age, were assessed for AN and cardiovascular risk factors using the office based **Expiration/Inspiration Ratio Test (E/I Ratio).** An abnormal E/I Ratio, a measurement of heart rate response to deep breathing, was indicative of parasympathetic nervous system damage. With continuous electrocardiogram monitoring, a one minute coached deep breathing exercise comprised of six maximal expirations and inspirations was performed. This procedure was repeated a second time. The E/I ratio was then calculated by determining the mean value of the longest RR interval from the electrocardiogram during expiration and the shortest RR interval from inspiration. An abnormal ratio was considered ≤ 1.1. Findings confirmed that

cardiovascular risk factors are correlates of AN (Maser et al., 1990). AN can be isolated or coexist with other diabetic complications or peripheral neuropathies, such as **distal symmetrical polyneuropathy (DSP).** In addition to a negative impact on survival, AN can also have a significant negative impact on quality of life.

Leading to this decline in their **quality of lif e (QOL)** , males with ED may also develop **depression** and/or anxiety which can impact negatively on their relationship with their spouse or partner (MacDonagh, Porter, Pontin, & Ewings, 2004). Themes resulting from qualitative research contributing to depression and/or anxiety include the male's sense of loss with regard to manhood, isolation and stigma associated with ED, and a sense of isolation with the problem (MacDonagh et al., 2004). Some of the males with ED expressed the lack of an acceptable "quick fix" to their "problem" and this lack in a "fix" to the ED was seen as a further source of anxiety (MacDonagh et al., 2004). The male perception of self control is also adversely affected by ED and admitting lack of control, confers a need for help. It also requires the man to expose his problem. Males with ED and diabetes are reluctant to do so in that they may be perceived as weak by their peers and partners (Jack, 2005). Since ED can be chronic, it is estimated that the cumulative effect on the quality of life is considerable (MacDonagh et al., 2004).

There is also an economic burden seen with T1D and ED. Direct costs and indirect expenditures attributed to diabetes in 2002 totaled $132 billion. Of the $91.8 billion spent for direct medical expenditures, $24.6 billion resulted from chronic complications due to diabetes, $23.2 billion for diabetes care and $44.1 billion for excess general medical conditions (Association, 2003). In addition, indirect costs, that is, money spent due to disability, work loss, restricted activity, and mortality due to diabetes totaled $39.8 billion (Association, 2003).

Those with diabetes had medical expenditures that were 2-4 times higher than expenditures for persons matched for age, sex, race/ethnicity without diabetes (Association, 2003). However, these are approximate estimates and considered to be underestimates of the true cost (Association, 2003). There is also an economic impact of ED that is not only limited to treatment and costs at diagnosis. There are subtle impacts that are difficult to quantify such as loss of work, decreased productivity due to psychological distress, and stress placed on the partner and family (Sivalingam, Hashim, & Schwaibold, 2006). Reported 1985 total direct costs for ED were $146 million (Wessells, 2007). Pharmaceutical sales for products for ED has risen from $0.9 billion in 1998 to $5 billion in 2002 (Sivalingam et al., 2006).

The information thus far has focused on the prevalence, burden and cost of diabetes and ED as well as the demographic and biological risk factors associated with ED. The following section presents behavioral and cognitive factors that could potentially prevent or delay the development of ED.

Data from the Diabetes Control and Complications Trial (DCCT) suggest that most complications can be prevented or delayed in onset by adherence to a diabetes regime of tight metabolic control (DCCT, 1990). This complex treatment regime includes insulin, diet, exercise and glucose monitoring. Cognitive factors, such as **knowledge** and **health beliefs (self-efficacy and perceptions of severity)** influence **self-management behaviors** (Glasgow, Ruggerio, Eakin, Dryfoos , & Chobanian, 1997). Intensive treatment reduced the risk of nephropathy, neuropathy and retinopathy by 35% to 90% compared to the conventional treatment. Although for specific manifestations like ED, this has not been directly documented (DCCT, 1998, 2002). Therefore, the public health burden of this disease and the development

of complications, such as ED, can be reduced by identifying and reducing risk factors and assessing self-management behaviors.

1.1 PROBLEM STATEMENT

Although ED is not considered life threatening, family planning problems and quality of life issues can result from this complication (DeBeradis et al., 2002). As mentioned, prevalence, the number of cases that are present, at or, during a specified period of time, for ED in males with T1D range from 27%-75% (Fedele, 1998; Klein, Klein, & Moss, 2005; Siu, Lo, Ip, & Wong 2001)For males with diabetes between the ages of 30-34 years, ED is present in approximately 15%, and increases to approximately 55% by age 60 years (Moore & Wang, 2006)..Males with T1D are twice as likely to develop ED than males without **diabetes**, (Bacon et al., 2002; http://www.diabetes.org/diabetes-statistics/complications.jsp, 2007; A Vinik et al., 2003)and at an earlier age, some as early as age 25 years. Risk factors for the development of ED in men with T1D are increasing **age**, a longer **duration of the T1D** , **poor metabolic control**, **smoking**, **alcohol intake,** selective **anti-hypertensive med ications**, **depression, hypertension**, and the **number and presence of other d iabetes co mplications** (Close & Ryder, 1995; Enzlin, 2003; Fedele, 1998; Klein et al., 2005) . These risk factors can be categorized as demographic, biological, psychosocial, behavioral and cognitive. Although several studies have estimated the prevalence and incidence of ED in males with T1D, there have been no studies that have fully detailed the sequence of developing ED in relation to risk factors and other complications. With regard to psychosocial factors, almost all studies have examined the effects of ED on the quality of life, depression, and anxiety rather than reversing

the temporal order and identifying pre-existing correlations. This study also is unique in its significance in that it has baseline data for QOL and depression prior to the development of ED and identification of other risk factors. Also, there have been no studies, to date, that have investigated longitudinally the self-management behaviors of males with ED and diabetes.

1.1.1 Purpose

Primary objectives of this study include: 1) to determine both the prevalence and incidence of ED in the Epidemiology of Diabetes Complications Study (EDC) population; 2) to identify risk factors for development of ED; 3) to determine the natural history of ED particularly if ED development occurs at a particular stage of neuropathic disease. The secondary objective is to identify longitudinal self-management behaviors of males with ED in the EDC as related to knowledge and health beliefs (self-efficacy, perceptions of severity of complications of diabetes).

The sample population will be males from the Pittsburgh Epidemiology of Diabetes Study (EDC). This is a NIH funded representative longitudinal study designed to follow a well defined T1D cohort to determine risk factors for the development of major diabetic complications. A potential eligible participant pool of 1,124 included those with T1D who had been either diagnosed or seen within one year of their diagnosis at the Children's Hospital of Pittsburgh between January 1, 1950 to May 31, 1980 who lived within 100 miles or 2.5 hours of Pittsburgh. Seven hundred eighty-eight participants (658 full participation and 130 survey information only) resulted from those eligible and baseline EDC examinations were completed for study participants during 1986-1988. Data were then collected biennially on this cohort, for a period of 20 years (1986-2006), by face-to-face clinic visits, physical assessments,

laboratory testing and self report. Collection of data continued to be ascertained in the 21st year (2007) of this longitudinal study by the above methods.

1.1.2 Specific Aims/Research Questions

The specific aims and research questions of this study were to:

Specific Aim #1: Determine both the age-specific ***prevalence*** and ***incidence*** of ***ED*** obtained by self-report during physician interview

Question #1a: What is the age-specific prevalence of ED for males enrolled at baseline as compared to age-specific normative data?

Question #1b: What is the age-specific incidence of ED?

Specific Aim #2: Determine baseline predictive risk factors for the development of ED.

Question #2a: Which baseline ***demographic factors*** (age, income, marital status, level of education**)** and ***biologic factors*** [HbA1c, age at diagnosis, duration of diabetes, E/I ratios, type and number of complications, systolic and diastolic blood pressure, lipid profile (High Density Lipoprotein (HDL) and non-HDL cholesterol)], ***lifestyle behavior*** (smoking, alcohol intake) and the use of ***anti-hypertensive medication*** *predict* prevalent and incident cases of ED?

Question #2b: Do baseline ***psychosocial factors*** [quality of life (modified DCCT-QOL Questionnaire), depression (Beck Depression Inventory)] predict ED?

Specific Aim #3 Determine the sequence of the development of ED in relation to other markers of neuropathy, i.e., Autonomic Neuropathy ***(AN)(*** E/I ratio <1.1), Confirmed Distal Symmetrical Polyneuropathy **(*CDSP*),** and Symptomatic Autonomic Neuropathy **(*SAN)*** (excluding ED) using longitudinal data.

Question# 3a**:** What is the sequence to the development of ED in relation to other markers of neuropathy, i.e., AN, CDSP, and SAN?

Secondary Specific Aim: Determine ***behavioral and cognitive risk factors***, as represented by self-management behavior, self-efficacy, perception of severity and knowledge associated with the development of ED using EDC self-reported longitudinal data.

Question #1.: Does self-management behavior, self-efficacy, perceptions of severity and knowledge of diabetes predict ED?

Question #2: Is self-management a mediator between cognitive variables (self-efficacy, perceptions of severity and knowledge) and ED?

1.2 DEFINITION OF TERMS

The following define the terms used throughout this dissertation:

Type 1 Diabetes (T1D) - insulin dependent diabetes mellitus.

Pittsburgh Epidemiology of Diabetes Complication Study (EDC)-longitudinal study conducted in Pittsburgh from 1986-2007 following a (youth onset of diabetes) cohort of individuals diagnosed with type 1 diabetes between 1950-1980, and evaluated at Children's Hospital of Pittsburgh within one year of diagnosis.

Erectile Dysfunction(ED)-sexual dysfunction resulting from autonomic neuropathy of diabetes and not due to any other medical or psychological problem or medical treatment as determined by the examining EDC physician.

Prevalence-the number of cases present at, or during a specified period of time (Lilienfeld, 1976).

Incidence-the probability, or risk, of developing the disease within a specified period of time (Lilienfeld, 1976).

E/I ratio-physiologic indicator of autonomic neuropathy (AN) defined as an abnormal heart rate response to deep breathing calculated by the mean value of the longest RR interval during expiration and the shortest RR interval during inspiration (abnormal reading : E/I ratio less than 1.1).

Symptomatic autonomic neuropathy (SAN)-E/I ratio less than 1.1 and 2 or more of the following clinical symptoms; postural hypotension, gastroparesis, diabetic diarrhea, colonic atony, genitourinary, sudomotor abnormality, or hypoglycemic unawareness as documented by physician exam.

Distal Symmetrical Polyneuropathy (DSP)-Clinically evident diabetic peripheral neuropathy confirmed by physician's exam defined as at least 2 of the following: 1) symptoms consistent with DSP; 2) abnormal sensory exam consistent with DSP; 3) decreased or absent deep tendon reflexes.

Confirmed Distal Symetrical Polyneuopathy (CDSP)-Clinically evident DSP (as described above) and vibratory threshold of >2.39 for ages < 36 years, >2.56 for ages 36- 50 years, and, > 2.89 for ages >50 years..

Social Cognitive Theory-Theory derived from the Social Learning Theory credited to Albert Bandura in 1962 that posits that behavior, cognition and environmental events operate as interacting determinants influencing each other bidirectionally.

Self-efficacy –Construct of the Social Cognitive Theory (SCT); perception that one possesses the capabilities to organize and execute the course of action required to produce prescribed outcome.

1.3 SIGNIFICANCE OF THE STUDY

Diabetes is one of the major chronic diseases seen today that imparts significant public health burden on society. Complications from diabetes are costly and result in excess morbidity and mortality. Understanding the long term complications of diabetes, the intra-relationships among these complications and the risk factors is important. It is with this understanding that complication rates will decrease and an improvement in the quality of life of those affected by diabetes will occur. Although ED is not considered to be a life threatening complication, the development of ED is associated with other more life threatening concurrent complications so there is necessity in investigating this further. Prevalence can estimate public health burden of a disease. However, these types of studies tend to underestimate total disease frequency. On the other hand, incidence can determine actual risk and likely causality and, serve as the basis for preventative services. Prior research has not documented the temporal relationship between risk factors and the development of ED. Since data from the Diabetes Control and Complications Trial (DCCT) suggests that complications can be delayed or prevented by achieving tight metabolic control, it is imperative that risk factors associated with ED be identified to focus intensification of therapy. Partial significance to this study results from determining the demographic and biological risk factors for the development of ED. However, adding additional significance to this study is determining the temporal relationship of the psychosocial risk factors as well.

Previously, published literature has focused on the physical aspects of ED. There is little research that focuses on the male's perceptions of his sexuality, self-efficacy and control of diabetes and their role in the development of ED (Jack, 2005). Typically what is applied to treating and educating males about diabetes is largely derived from studies in which females

dominate the population (Hardy & Bell, 2004 ; Jack, 2005) Since diabetes treatment is a cooperative process, there is necessity to understanding the self-management behaviors of males in relationship to the development of ED. This study is also appropriately timed in that it coincides with a national effort to engage men in addressing health issues.

The *mission of the American Diabetes Association is to prevent and cure diabetes and to improve the lives of all people affected by diabetes.* The significance of this study is in 1) further examine the prevalence and incidence of ED attempting to understand the temporal relationship between the risk factors and the development of ED and, 2) exploring the self-management behaviors of those with ED. Findings of this study could potentially raise awareness and understanding of the risk factors in the development of ED in an attempt to modify the risk of developing this complication.

2.0 REVIEW OF THE LITERATURE

2.1 INRODUCTION

The relationship between diabetes and sexual problems has long been recognized. Avicenna, who lived between the years of 960-1037A.D., was the first to mention the "collapse of sexual function" as a specific complication of diabetes in his medical encyclopedia (Enzlin, 2003). Estimates are that 50-70% of all males with diabetes will develop a functional sexual disorder in which the primary complaint is erectile dysfunction (Enzlin, 2003). Prior community research reports the **prevalence** of ED to be within the range of 10% to 52% (Laumann, Paik, & Rosen, 1999) while 10 year overall **incidence** of self-reported ED was 25% in males 21 years of age and older with 10 or more years duration of T1D (Klein et al., 2005). ED in males with diabetes develops at an earlier age than the general population , can occur as early as age 25 and can cause significant family planning problems.

ED is a multifaceted disease, having potential psychological, neurological or vascular etiologies, seen not only in the general public but also as a complication of T1D. The following is an extensive review of the literature describing the physiologic etiology of ED, the epidemiology of ED, identification of the demographic, biologic, lifestyle behavioral psychosocial risk factors, cognitive risk factors, and their interrelationships in the development of ED, a review of T1D, and the epidemiology of diabetes and complications.

Studies on the physiological mechanisms of ED have been documented throughout history. To evaluate the erectile process, modern neurological techniques are documented in the literature dating back to Eckard in 1863 (Stief, 2002). Even though the research continued in physiology, the psychological theories became the front runners as the etiology of ED, and, especially dominated medicine as a result of the work completed by Sigmund Freud. In the 1940's, Joslin remarked on ED , " *a rare complaint that is best purposely neglected because it may disappear with general improvement of therapy, or if not, the less the attention of the patient is directed to it, the better."* This philosophy of treatment prevailed until Kinsey in the late 1940's openly discussed aspects of male sexuality (Sullivan et al., 1997). The last 15 years have provided advanced molecular and pharmacological studies that have enriched the body of knowledge in the pathophysiology and pharmacotherapy of erectile disorders. Although today, the exact etiology is still not yet known, research continues. A brief review of this literature was presented. Because within this literature lies the physiological rationale for the present treatment options available to males with ED, both with and without diabetes.

"*Probably the most clinically significant epidemiological task is the determination of risk factors because of the implications for intervention of modifiable risk factors and for patient screening*" (Maser et al., 1991). By reviewing both epidemiology of ED in those with and without diabetes the possible interrelationships for risk are determined.

T1D is a disease that manifests a global burden on society. Estimates are that the incidence of T1D will continue to increase. If ED can be prevented or delayed in occurrence, then it is in the public health interest that issues surrounding self-management behaviors and self efficacy be explored as well. Therefore, a review of the literature is necessitated for these areas as well.

2.1.1 Anatomy of the Penis

The male penis is an external genital organ having a sexual and urinary function. It is attached to the pubic symphysis by two ligaments and located above the scrotum. There are three cylindrical bodies of erectile tissue within the male penis: one ventral corpus spongiosum (wherein lies the urethra), and two corpora cavernosa located side by side in the dorsal half of the penis. A thick bilayer fibrous sheath, called the tunica albuginea, encloses the corpus cavernosa. These fibers unite medially forming a septum which allows the two corporal cavernosa bodies to function as one unit. The corpus spongiosum also has a somewhat thinner tunica albuginea. Deep fibrous and resistant tissue called Bucks fascia , surrounds all three corporal bodies (Kirby, Culley, & Goldstein, 1999; Meeting, 2003; Melman & Gingell, 1999). Lacunar spaces, a lattice of vascular sinusoids, are lined with vascular endothelium. These comprise the erectile tissue and are surrounded by a trabecular of smooth muscle fibers with an extracellular matrix of fibroblasts, elastin and collagen.

Penal blood supply is from a branch of the hypogastric artery called the internal pudendal artery which divides to form the cavernosal, the dorsal, the bulbar and the urethral arteries. The cavernosal artery is the main blood supply to the corpora cavernosa. This artery divides further into the helicine arteries whose branches open into the cavernosal spaces. Venous drainage occurs through the superficial, intermediate and deep veins (Kirby et al., 1999). It is the deep veins that drain the corpora cavernosa and the corpus spongiosum (Melman & Gingell, 1999).

Innervation of the penis is autonomic (parasympathetic and sympathetic) and somatic (motor and sensory). The parasympathetic nerves arise from neurons in the sacral spinal chord, whereas, the origin of the sympathetic nervous system is the thoracolumbar spinal

chord. These enter the corpora cavernosa and corpus spongiosum to affect the neurovascular events of erection and detumescence. Innervation by somatic nerves, namely the pudendal nerve, to the bulbocavernosus and ischiocavernosus muscles, is responsible for sensation to and contraction of the penis (Dean & Lue, 2005).

2.1.2 Physiology of the Penile Erection

The physiology of penile erection and detumescence are active neural-hemodynamic events regulated by contraction and relaxation of corporal smooth muscles. There are three types of stimuli for erection, namely, *reflexogenic (*genital stimulation), *nocturnal* (post rapid eye movement sleep) and *psychogenic or central* (can be multiple or single psychological stimuli). The flaccid state is caused by predominate sympathetic influence in which the corporal and arterial muscles are contracted. There is minimal blood flow as a result to the cavernosal spaces from the cavernosal artery. After an initiation by a psychogenic stimuli (sexual, desire, perception) ,there is a release of neurotransmitters from the cavernous nerve terminals (Conference, 1993). This stimulus to the parasympathetic system causes a decrease in peripheral resistance from vasodilatation and an increase in the blood flow through the cavernous and helicine arteries further causing an increase in intracavernous pressures. This then traps the incoming blood by the expanding sinusoids causing compression of the subtunical venular plexuses which lies between the tunica albuginea and the peripheral sinusoids thus reducing venous outflow. The tunica is then stretched to its capacity occluding the emissary veins between the outer longitudinal and inner circular layers further decreasing the venous outflow. The full erection phase, also referred to as the venous occlusive mechanism, occurs when there is a PO_2 increase to around 90mmHg and an intracavernous

pressure increase of around 100mmHg. There is an increase in intracavernosal pressure above systemic pressure due to contraction of the ishiocavernous and bulbocavernous muscles. During the rigid erection phase there is a further increase in the pressure with resultant contraction of the ischiocavernosus muscles and cessation of blood flow through the cavernous artery. In summary, erection involves; 1) relaxation of the sinusoids, 2) arterial dilatation and 3) rapid venous compression.

There are three phases of detumescence. The first phase includes a transient increase in intracorporeal pressure causing the beginning of smooth muscle contraction against a closed venous system. Detumescence is caused by increased sympathetic nervous system activity with resultant increases in helicine artery tone and trabecular smooth muscle contraction. During the second phase there is a decrease in pressure allowing the re-opening of the venous pathways and return of basil arterial flow. In the final and third phase there is full restoration to the venous outflow capacity after a rapid pressure decrease due to venous-occlusive mechanism deactivation (Dean & Lue, 2005; Kirby et al., 1999; Melman & Gingell, 1999).

Erection begins in the brain. Integration of the stimuli occurs at the limbic system, hypothalamus and brainstem (Christ & Hodges, 2006). Stimulation to the autonomic nervous system of the penis by the sacral (S2-S4) parasympathetic cavernous nerves is responsible for initiating an erection (tumescence) whereas stimulation to the thoracolumbar (T11-L2) sympathetic nerves is responsible for detumescence (Dean & Lue, 2005). The pudendal nerve sends the sensory signals to the spinal chord to the appropriate brain centers. Several areas within the central nervous system play a role in the process of erection. Those most studied include the paraventricular nuclei, the medial preoptic area and the hippocampus areas (Kirby et al., 1999). Neurotransmitters released as a result of sexual stimulation that are excitatory are

acetylcholine, serotonin, oxytocin and dopamine. Major neurotransmitters that are inhibitory include epinephrine, norepinephrine, gamma aminobutyric acid and prolactin. Corporal smooth muscle cell tone then, is the response of complex integration of the effects of the neurogenic-origin neurotransmitters and the endothelial-origin neurotransmitters.

The release of the neurogenic-origin neurotransmitter norepinephrine causes activation of the post-synaptic α1-adrenergic receptors by the sympathetic nervous system causing smooth muscle contraction and erection. A second neurotransmitter, nitric oxide (NO) or nitric oxide releasing substance, previously known as endothelium derived relaxing factor, induces smooth muscle relaxation (Melman & Gingell, 1999). NO is produced from an amino acid, L-arginine, thru the enzymatic action of nitric oxide synthase (NOS). There are two endothelial forms of NOS, namely cNOS; type III, and iNOS: type 1. There is also one neural form (nNOS;type 1) which is of importance to the non-adrenergic, non-cholinergic(NANC) autonomic nerves that innervate penile erection tissue causing vasodilatation (Klabunde, Ryan, & Paxson, 2007). Nitric oxide is the first neurotransmitter produced by nitric oxide synthatase that is released into the non-adrenogeric, non-cholinergic nerve terminals and into the endothelial cells that line the corporal sinusoids. NO initiates the erection process and mediates penile vasodilatation by converting quanosine triphospate (GTP) into cyclic guanidine monophosphate (cGMP second messenger) via the enzyme guanylyl cyclase. cGMP is responsible for activation of protein kinase G (PK-G). As a result of the activation of PK-G, calcium channels are affected resulting in an alteration of calcium sensitization, decreased intracellular calcium and diminished corpora cavernosa smooth muscle tone thus enabling erection to occur (Christ & Hodges, 2006; Meeting, 2003; Pegge et al., 2006).

Mediating detumescence is the release of acetylcholine by the parasympathetic nervous system. A decrease in the nitric oxide release and inactivation of the second messenger(cGMP) causes detumescence (Meeting, 2003; Melman & Gingell, 1999).

2.1.3 Pathophysiology of Erectile Dysfunction

Erectile dysfunction (ED) is defined as *the persistent inability to obtain and/or maintain a penile erection sufficient for satisfactory sexual activity* (Conference, 1993; Jardin et al., 2000). In order to establish this diagnosis, ED must be present for a minimum of least 3 months. There is an exception to this if ED if preceded by pelvic surgery or penile trauma.

For normal erectile function to occur there is a need for a delicate balance between vasoconstriction and vasorelaxation of the corporal smooth muscle. There must occur a critical level of relaxation or there will be incomplete resistance to the outflow of blood from the corpora causing a spectrum of penile tumescence ranging from flaccidity to non-complete erection (Kirby et al., 1999). This incomplete corporal smooth muscle relaxation, termed veno-occlusive dysfunction, may have multiple etiologies. Since it is widely recognized that erections combine neurovascular phenomena and vascular biologic responses, ED may result from an interruption of any of the natural sequencing mechanisms. In addition, hormonal stimuli, biomechanical mechanisms, or localized biochemical reactions influence neurovascular control.

Several classification systems have been proposed for ED. Based on the cause of ED, ED can be classed by neurovascular mechanisms of penile function, i.e., neurogenic (failure to initiate), arterial (failure to fill), or, venous (failure to store) (Dean & Lue, 2005). The International Society of Impotence Research recommended the following classification:

psychogenic or organic (Dean & Lue, 2005; Lizza & Rosen, 1999). This taxonomy for ED by the International Society for Sexual and Impotence Research has deleted the term *psychogenic* and categorizes ED as either *situational* or organic (Sachs, 2003). Situational ED results in certain environments, with certain partners or under certain circumstances (Lewis, 2004). Currently, ED is seen as exhibiting both psychogenic and organic factors frequently referred to as *mixed.*

2.1.4 Psychogenic Causes of ED

Prior to 1980, approximately 90% of ED cases were thought to be psychogenic in origin. The limbic system, the hypothalamus and the cerebral cortex control sexual behavior and penile erection. Thus, messages that are either stimulatory or inhibitory can be relayed from the spinal centers with resultant erection or erection inhibition. There are two mechanisms that may explain erection inhibition in psychogenic dysfunction. These two are as follows:1) In an anxious man, there may be elevated peripheral catecholamines causing an increase in smooth muscle tone preventing relaxation necessary for erection or, 2) there is a direct inhibition to the spinal centers within the brain by excessive sympathetic outflow. By stimulation of the sympathetic nerves or systemic epinephrine influence, detumescence results.

Several common causes of psychogenic ED are recognized and include (Kirby et al., 1999; Weeks & Gambescia, 2000);

- Depression
- Sexual Inhibition
- Performance Anxiety
- Relational conflict/loss of attraction

- Sexual Abuse in Childhood
- Conflict over sexual preference
- Fear of Pregnancy or sexually transmitted diseases (Kirby et al., 1999)

2.1.5 Organic Etiologies of ED

2.1.5.1 Arterial ED

Atherosclerosis is the most common cause of vasculogenic ED (Blumentals, Gomez-Caminero, Joo, & Vannappagari, 2003; Meeting, 2003). Investigationally, it has been shown that obstructing the arterial inflow to the corporal bodies by atherosclerotic lesions is associated with ED. Atherosclerotic lesions, produced by feeding rabbits a high cholesterol diet, resulted in vasculogenic ED. These cause an obstruction , or limit to in the blood flow from the iliac arteries (Saenz de Tejada et al., 2005). Angigraphically shown, ED occurs when more than half the lumen of the internal pudendal, common penile and cavernosal arteries are narrowed. Mechanisms of atherosclerosis morphologically include vascular smooth muscle cell proliferation, endothelial injury, and cellular migration. Cytokines, atheroma, metabolic alterations (i.e. diabetes), thrombosis, blood components, growth factors, antioxidants, heparin sulphate and gene mutations (eg., apolipoprotein E, and lipoprotein lipase) are factors that influence these changes (Sullivan, Keoghane, & Miller, 2001).

One category of risk factors is demographic in nature. A strong risk factor for the development of atherosclerosis is **age**. In the rat penis, age has been shown to correlate with altered nitrous oxide (NO) synthesis and erectile responses (Garban, Vernet, Freedman, Rajfer, & Gonzalez-Cadavid, 1995). As a compensatory mechanism to endothelial dysfunction associated with aging, Haas et al (Haas et al., 1998) have shown an upregulation of

endothelial NO synthase (eNOS) in aging rabbits' corporal smooth muscle cells and endothelium with impaired endothelial-mediated cavernosal relaxation.

Endothelial cell dysfunction, defined as an abnormal endothelial response causing reduction in the bioavailability of nitric oxide (NO) leading to impairment in vasodilatation, results in failure of the smooth muscles lining the arterioles to relax (Montorsi, Briganti, Salonia, Rigatti, & Burnett, 2006). Endothelial NO modulates vascular tone at rest, vasodilatation during stress and inhibits platelet aggregation. Thru inhibition of platelet aggregation, there is activation of intracellular guanlate cyclase, which then generates cyclic GMP. Endothelial dysfunction is considered important in the pathophysiology of ED because of the vasodilatation and effects on smooth muscle proliferation. The cardiovascular risk factors **of hypertensio n, diabetes mellitus, smoking** and **dyslipid emia** are linked to endothelial dysfunction and are often present in those presenting with ED as well. It is also theorized that endothelial dysfunction is the initiating event in atherosclerosis and is also linked to ischemic coronary disease.

2.1.5.2 Neurogenic ED

Approximately 10%-19% of ED is neurogenic in origin (Dean & Lue, 2005; Saenz de Tejada et al., 2005). There are three etiologies of neurogenic ED as follows; 1) Peripheral (peripheral ED), 2) Spinal (sacral-peripheral, suprasacral-central ED), and 3) Supraspinal (suprasacral ED) (Saenz de Tejada et al., 2005). Disorders that affect the peripheral efferent autonomic nerves or the parasympathetic sacral spinal chord can cause complete or partial ED by compromising relaxation of the corpora cavernosa smooth muscle fibers (Kirby et al., 1999; Meeting, 2003; Sullivan et al., 2001). Central origin ED can originate from lack of excitement or an increase in inhibition of central autonomic pathways (Saenz de Tejada et al., 2005). Men who sustain

spinal chord injury can have erectile dysfunction. The level of the spinal chord injury determines the degree of erectile function. Injuries to the upper portion of the spinal chord results in the likely retention of erectile function where as injuries to the lower chord results in unlikely erectile function. Several other diseases are associated with ED that include multiple sclerosis, and peripheral neuropathy due to alcoholism or diabetes mellitus, tumors, disk disease and transverse myelitis (Kirby et al., 1999). Because of the close proximity of the cavernous nerves and the pelvic organs, surgery in these anatomical areas can cause neurogenic ED as well. Another neurogenic cause is pelvic fracture.

2.1.5.3 ED related to toxins and drugs

It is estimated that one in every four males presents with ED because of a drug related problem. Cocaine use and long term excessive **alcohol consumption** have been linked to ED (Kirby et al., 1999; Meeting, 2003). It is known that over 100 commonly prescribed medications can affect /alter sexual desire, erection and/or ejaculation. Antianxiety agents, antidepressants, antipsychotics**, antihypertensive agents** , diuretics, and antiandrogenics are examples of these medications. **Smoking** can cause an imbalance between thromboxane and prostacyclin concentration thus causing a direct toxic effect on the vascular endothelium resulting in ED.

In summation of the above review, the demographic risk factor (age), the biologic risk factors (diabetes, dyslipidemia, hypertension), lifestyle behavioral risk factors (smoking, alcohol consumption), and, anti-hypertensive medications have been supported physiologically in their relationship to the development of ED.

2.1.6 Epidemiology of Erectile Dysfunction

When reviewing the literature concerning the epidemiology of ED, it is important to note the population from which the data were generated. There were two fundamental methods used to ascertain the samples, each presenting with strengths and weaknesses in design. The first, the clinical study, recruited those patients who presented for a specific reason of sexual dysfunction. Although this type of sample generated opportunities to collect information lending to understanding complex etiologies of ED through the use of sophisticated diagnostic procedures and comorbid conditions in those presenting with the disease, they are highly biased and result in data that is selective and an underestimate of the actual disease prevalence (Rothman, Greenland, & Lash, 2008). The second method used population based probability survey sampling techniques. Those recruited were from representative population samples. These studies relied on self-report that are also known to present reliability and validity issues. Under-reporting, particularly of ED, can occur because of concerns for social stigmatization that sometimes accompanies ED (Rothman et al., 2008). Also contributing to under-reporting is the fact that particularly as males age there is belief that ED can be part of the aging process and therefore ED is under-played. In essence then both sample designs result in an underestimation of ED and probably account for the differences in prevalence rates reported in the literature.

In addition, prior to the 1993 standardization of the definition for ED, ED was included in the overall definition of impotence, which also captured other male sexual function disorders, and ejaculatory and orgasmic dysfunctions (Melman & Gingell, 1999). This then also affected the reliability and validity of the studies under review. Therefore, when

completing a review into the epidemiology of ED, the prevalence of ED generated by these previous studies should be viewed with caution.

Research completed by Kinsey, in the 1940's, was one of the first if, not most famous studies focusing on male sexual problems. Kinsey et al (Derby, Araujo, Johannes, Feldman, & McKinlay, 2000) relied on a volunteer population from an ill-defined region in Illinois to study sexual phenomenon. Since it is known that volunteer samples can potentially present bias (Rothman et al., 2008), this study can only be used as suggestive and will not be discussed in this review. Furthermore, the definition of ED was not consistent with the present parameters recommended by the NIH Consensus Conference. There are however, two other population based samples completed within the United States worth discussing in this literature review; the Massachusetts Male Aging Study (MMAS) and the National Health and Social Life Survey (NHSLS).

The MMAS provided information on the **prevalence** of ED from a random community based sample of 1290 males between the ages of 40 and 70, conducted between the years 1987-1989 in cities near Boston Massachusetts. The definition of ED was assessed from a sexual activity questionnaire that asked specific questions concerning frequency and quality of erection. Using probabilities proportion to the population, communities were randomly selected within each of six strata for this prospective observational study. The strata were defined by community size and income. Response rate was 52%, however, participants were similar to men aged 40 to 70 from the Third National Health and Nutrition Survey with respect to comorbid conditions of diabetes, hypertension, weight issues and smoking behavior, and therefore findings are considered somewhat valid. The MMAS was not considered racially balanced by US Census Bureau standards, in that there was only 5% participation by racial

minorities but was however considered overall to be consistent with the Massachusetts 1990 population for males 40-69 years of age. In the subject' s home, by trained interviewers, information on health status, medications, life style, socio-demographics, psychological indexes and blood samples were obtained. Sexual activity information was ascertained from a self-administered questionnaire. Prevalence for combined minimal, moderate and complete impotence was 52%. Between 40 and 70 years of age, **p revalence** of complete impotence tripled from 5% to 15%. The strongest predictor of impotence was the participant's **age** and the overall prevalence rate after longitudinal follow-up of this population was 24%. **Incident** ED figures for the 40 year old age group was 10.3%annually , while the incident rates for the 50 year old and 60 year old age groups were 25.5% and 38.4% annually respectively (Araujo, Johannes, Feldman, Derby, & McKinlay, 2000). After adjusting for age, higher probabilities of impotence were positively correlated with **diabetes, heart disease** , indexes of anger and **depression,** and, **hypertension**. Index of dominant personality and **HDL-cholesterol** were inversely correlated with impotence. There was a greater probability of complete impotence in men with heart disease and hypertension associated with **cigarette smoking** (Feldman, Goldstein, Hatzichristou, Krane, & McKinlay, 1994). Prevalence of diabetes in this sample was 7.8%, high blood pressure was 30.3%, 40.1% were overweight and 24.4% were current smokers (Aytac, Araujo, Johannes, Kleinman, & McKinlay, 2000). Findings from this study also confirmed that ED is inversely associated with **income** and **education**. A significant association for socioeconomic factors and ED was found for the occupation only after adjusting for age, lifestyle and medical comorbidites. Although this study focused on specific erectile function only, it was one that identified potential risk factors, associated comorbidites and socioeconomic factors for further study. Projected data from this study (Johannes et al.,

2000) suggest that there can potentially be 617,715 new cases occurring annually in US white males between the ages of 40-69. It is alarming to note that by the year 2025 the world projections for ED exceed 320 million cases (Aytac, Mckinlay, & Krane, 1999). Therefore, the MMAS confirmed the prevalence in the male population and identified significant risk factors with ED. Based on this study then, demographic factors (age, income, marital status, level of education), biologic factors (hypertension, dyslipidemia), lifestyle behavioral (smoking, alcohol) and psychosocial factors (depression) were examined in our analysis.

The NHSLS was a national probability survey of 1410 men between the ages of 18 and 59 years residing in United States households in 1992 of which there was greater than a 79% completion rate. Sexual dysfunction was reported in 31% of the 1410 males enrolled. Sexual dysfunction was indexed to seven dichotomous items, each measuring a critical problem or symptom in the past 12 months. Those who reported emotional or stress related problems were more likely to report sexual dysfunction as was deterioration in ones socioeconomic position. Found also in this survey was that **age** was a strong predictor of sexual dysfunction (Laumann, Paik, & Rosen, 2007). The association between race and ED was also reported. For blacks the adjusted Odd's Ratio of reporting an inability to achieve orgasm was 1.14 (95% C.I. 0.57-2.26), Hispanics was 1.24 (95% CI, 0.54-2.83) and for 'others' was 2.83 (95% CI, 1.24-6.50, $p<0.05$) with whites as the referent statistical group (Laumann et al., 2007). The NHSLS also confirms the risk associated with age and income. Stress and race as risk factors were additional risk factors identified by this study. Race and stress were not two variables of interest for study. The Pittsburgh-EDC male population was 99% Caucasian. Therefore, race was not considered for this analysis.

Another study of interest includes one that generated **age specific prevalence** and correlates from the Health Professionals follow-up study. This was a selected occupation based study. There were a total of 31,742 male dentists, optometrists, osteopaths, podiatrists, pharmacists and veterinarians in the United States who self-reported erectile dysfunction and were between the ages of 53 to 90 years. Fewer than 2% of the men reported ED before age 40, 4% reported ED between 40 and 49, 26% in men ages 50-59 years, and 40% in males 60-69 years. For males younger than 60 years and with **comorbid conditions**, the prevalence was twice that of healthy men. Of note, physical activity and ED was explored in males within this group. Younger men who were less than 60 years benefited more from physical activity than do men greater than 80 years. Negative health behaviors, watching more than 20 hours of TV per week, and **smoking** were more strongly associated with ED with younger males being at increased risk (Bacon et al., 2003). Comorbid conditions of diabetes, cancer, stroke and hypertension were also associated with ED among these study participants. In summary of the Health Professionals Follow Up Study then, age specific prevalence rates were generated for age groups of 10 year increments starting at age 40 years and demographic risk factors (age,) biologic risk factors(diabetes, cancer, stroke, hypertension), lifestyle behavioral (smoking, physical activity). As stated previously, this study will assess the demographic risk factor of age, the biologic risk factors (hypertension, cerebral vascular disease) and the lifestyle behavioral risk factor (smoking). Physical activity will not be assessed. Age-specific prevalence rates were generated.

In a retrospective cohort study of a representative national managed care database of 51commercial health plans and 28 million members in the United States, Sun et al (Sun et al., 2006) found 285, 436 males reported an ED diagnosis from 1995-2001. The following table

illustrates the region adjusted prevalence rates by age and for concurrent diseases of hypertension, hyperlipedemia, diabetes mellitus and depression.

Table 2. 1 Re gion Adjusted Prev alence Ra tes (2000 Censu s Stand ard) by Age, and Conc urrent Disease (A. D. Seftel et al., 2004)

Age group (years)	% with ED	% of age group with Hypertension	% of age group with Hyperlipidemia	% of age group with Diabetes Mellitus	% ofage group with Depression
18-24	0.8	4.3	3.9	2.6	14.4
25-35	4.9	10.6	12.1	7.0	15.9
36-45	16.1	23.8	26.4	13.1	16.1
46-55	35.7	39.3	41.3	19.4	13.3
56-65	35.3	51.3	51.8	23.4	8.9
66-75	5.2	61.4	51.0	27.8	5.8
76-85	1.9	66.3	48.2	25.7	7.5
86+	0.2	63.0	30.3	22.3	8.0

Overall, the region adjusted prevalence rates for hypertension were 41.2%, hyperlipedemia was 41.8%, diabetes mellitus 19.7% and depression 11.9%. Because this database review was from managed care records excluding the aged population of males on Medicare, the hypothesis that ED increases in prevalence with increasing age was not as strongly shown as with the previous studies. More interestingly however, this study looked at ED as a marker for diabetes. Unadjusted prevalence rate for males having diabetes and ED was 20.0% while for those without diabetes was only 7.5%. After adjusting for age, census region, and 7 concurrent diseases, men with ED are still 60% more likely to have diabetes than men without ED as reflected in the calculated Odd's Ratio of 1.6, $p<0.001$(Sun et al., 2006). Interpretation of these results reinforces that ED and diabetes mellitus, hypertension,

hyperlipidemia and depression share common risk factors. (The definition of diabetes mellitus, however, in this review included both types of diabetes.) In addition, this study identified a psychosocial risk factor of depression.

In concluding this section, it is also necessary to briefly discuss the findings of the cross-sectional survey on Men's Health Issues, the MALES Study, a multinational study that included a male cohort, ages 20 to 75 years from Germany, United States, United Kingdom, France, Italy and Spain. The sample was geographically distributed with recruitment in 22 regions from the United States, 6 from the United Kingdom, 4 from Germany, 16 from Italy, 11 from France and 7 from Spain. The survey was completed on males presenting to health care professionals (general practitioners) between March and September, 2000. There were two planned phases to the study. First, while in the physician's office, a general questionnaire was given to the participants eliciting items of sexual health in order to ascertain the overall prevalence of ED in the population. With the first questionnaire, the males were asked to provide their names and addresses in order that a second questionnaire could be mailed to them to ascertain more detailed information concerning ED. However, because of the personal nature of the subject matter, the males were reluctant to provide follow-up information. The males identifying ED by first questionnaire while in the physician's office were therefore asked to complete a second questionnaire anonymously. Recruitment also was quite difficult in 4 of the 6 countries (Italy, Germany, France and Spain). Because these countries were having recruitment difficulties by using the general practitioner's office, Germany, Spain and Italy recruited from urology offices, while France recruited men from the street. Collection rates for the questionnaires were 51% for phase 1 , while phases 2 and 3 only yielded collection rates of 18% and 31% respectively. There were a total of 28, 691 across all 6 countries who provided

answers for the first questionnaire. Overall prevalence for self-reported ED across the 6 countries was 19%. Prevalence in the United States was approximately 23 % (6,474 / 28,691) while prevalence rates for France, Germany, Italy , United Kingdom and Spain were lower ranging from 12% to 19%. ED was again found to increase with age as previous studies reported. Age specific prevalence rates for males 70 to 75 years of age, ranged from 39 % to 73%. There was a 14 fold higher relative risk for this age group as compared to the 20 to 29 year age group. Less than 10% of the ED cases were in males younger than 40 years. Reported also was a positive correlation between ED and increasing poor health. Those respondents who reported poor health were 5 times more likely to report ED than those reporting excellent health. Also there was significant association between ED and lower urinary tract symptoms and ED and hypertension (Rosen et al., 2004).

The cost and burden of ED are still elusive. Tan et al (Tan, 2000) used a decision analytical model to forecast ED care in a health plan of 100,000 members, in 2000. The estimated cost was $3, 204, 772.00 (Tan, 2000). Many health plans today do not cover the cost of ED care (Sun, Seftel, Swindle, Wenyu, & Pohl, 2005). From review of the 285, 436 males who reported ED in the Sun et al (Sun et al., 2005) medical record review study; $83.91 was spent in 1999. This increased to $95.41 in 2000, and in 2001, $119.26 was spent by each patient for ED care. Review of the 2001 health care expenditures for ED revealed the following; 37% of costs were spent on PDE-5 inhibitor therapy, while 14 % of cost was for physician office visits, followed by 11% spent on diagnostic procedures, 8.5% on testosterone hormone therapy, 4% on penile implants, 4 % on intracaveronous injections, 2.7% on alprostadil insertion and 0.8% on vacuum erection devices (Sun et al., 2005).

In summary, review of the previous studies noted that there was 1) an underestimation of **prevalence** either due to limitations of study design or reluctance of males to discuss sexual function, 2) limited studies on **incidence**, and 3) the demographic risk factors associated with ED were increasing **age,** race, **income, marital status, level of edu cation,** biologic risk factors of diabetes mellitus, **hypertension**, **hyperlipidemia**, psychosocial risk factors of **depression,** lifestyle behavioral risk factors of **smoking** and **alcoh ol inta ke** and**, anti-hypertensive medications**. There was data for all the variables listed on males enrolled in the EDC, therefore all of these were included in the analysis.

2.1.7 Type 1 Diabetes

Diabetes mellitus is defined as *a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (MellitusEXpertCommittee, 2003).* T1D accounts for 5-10% of all diabetes cases diagnosed annually within the United States (ADA, 2007). As previously mentioned, T1D is the most common chronic metabolic childhood disease.

In T1D, formerly known as insulin dependent diabetes or juvenile onset diabetes, there are two distinct types identified: immune-mediated diabetes and idiopathic diabetes. Cellular-mediated autoimmune destruction of the beta cells of the pancreas is the etiology of immune mediated diabetes. Islet cell antibiodies (ISAs), antibodies to insulin (IAAs), autoantibodies to glutamic acid decarboxylase(GAD) and autoantibodies to the tyrosine phosphatase (IA2 and IA2 β) are all markers of immune destruction of the β cells. In 85-90% of all who present with hyperglycemia, one or more markers are present (MellitusEXpertCommittee, 2003). B cell destruction rate is variable. In mainly infants and children, the rate of destruction is rapid

while slow in others. The later group compromises mostly adults. Infants and children present with ketoacidois as the first sign of the disease while others may have hyperglycemia that when challenged by stress or infection converts to ketoacidosis. Adults in particular may have residual β cell function that is sufficient to delay ketoacidosis for many years. Treatment for this type of diabetes is insulin and necessary for survival.(MellitusEXpertCommittee, 2003) There are multiple genetic predispositions that have been posited as causal for this form of diabetes. There exists an extensive body of knowledge that cites importance to the role played by genetics. In more than 95% of people diagnosed with T1D, the Human Leukocyte Antigen (HLA) markers on the short arm of chromosome 6 , DR3 or DR4 are present (Haverkos, Battula, Drotman, & Rennert, 2003). The DR2 haplotypes are associated with lower risk for type 1 diabetes (Haverkos et al., 2003). The genetic component appears to present increased disease susceptibility however only one in five children with a first degree relative and only 1 in 15 children in the general population with identified high risk alleles will develop diabetes(Haverkos et al., 2003) . The DR2 haplotypes are associated with lower risk for type 1 diabetes. Therefore, there are additional environmental agents playing key roles in the development of diabetes. Positive linkage has been attributed to enterovirus infection (Haverkos HW, 2003). Other environmental agents investigated as possibilities in the development of T1D are chemical toxins, and nutritional and dietary factors.

The second type of type 1 diabetes is termed idiopathic diabetes and this type has no known etiology. There is no evidence of autoimmunity in this type. This type affects only a minority of the cases and most affected are of Asian or African ancestry (ADA, 2007). Idiopathic diabetes is inherited, is lacking in immunological evidence for β cell autoimmunity,

and is not associated with HLA. This form of diabetes requirement for insulin varies (ADA, 2007).

Diabetes is a life threatening disorder that requires a complex self-management treatment regimen requiring daily insulin, dietary restrictions, exercise and close blood glucose monitoring for survival and prevention of complications. Understanding and regulating blood sugar is key for managing this disease.

Complications: Excess morbidity and mortality in diabetes is due to long term complications. The complications of diabetes are usually categorized as either microvascular or macrovascular in origin. Both are thought to occur as results of long-term dominate effects of hyperglycemia. Previous research however has shown that despite maintaining euglycemia, risk of developing complications may only be reduced and not totally eliminated. (Stella, Tabak, Zgibor, & Orchard, 2006). Microvascular complications, which include retinopathy, neuropathy and nephropathy, are thought to occur as a result of long term glucose assault on the small blood vessels, while macrovascular complications produce large vessel disease associated with atherosclerotic lesion development. Macrovascular complications include cardiac, cerebral and peripheral vascular disease. Brief reviews of these complications follow. A more detailed review of diabetic neuropathy is presented since ED, the complication of interest in this dissertation, is associated with diabetic autonomic neuropathy.

Nephropathy: In the United States, this complication is the leading cause of end stage renal disease (ESRD) resulting in approximately 28,000 new cases diagnosed per year. A 2.2 % cumulative prevalence at 20 years and 7.7% at 30 years following diagnosis of diabetes were reported from Finne et al (Finne, Reunanen, Stenman, Groop, & Grönhagen-Riska, 2005) (Daneman, 2006). The stages of progression of diabetic nephropathy include 1) early detection

of microalbuminuria defined as *urinary albumin excretion rate >20ug <200ug per day* to 2) overt macroalbuminuria of *>200mg per day* with renal dysfunction to 3) ESRD. Microalbuminuria is predictive of advanced nephropathy in that there is a 50-66% probability of progression once detected (Daneman, 2006).

Retinopathy: There is a 20-25% prevalence rate of proliferative retinopathy in type 1 diabetes. The early stage includes mild non-proliferative diabetic retinopathy defined as *retinopathy having increased vascular permeability*. This stage clinically is manifested by "cotton wool" spots. The middle stages include 1)moderate non-proliferate diabetic retinopathy which is manifested by intraretinal microvascular abnormalities , 2) severe non-proliferative retinopathy which is retinal capillary loss, and 3) very severe non-proliferative diabetic retinopathy evident by *retinal ischemia, or extensive intraretinal hemorrhage and presence of microaneurisms.* Late stage is proliferative diabetic retinopathy and is the leading cause of blindness. Predictors of retinopathy include hyperglycemia, longer duration of diabetes, and hypertension. There is also an association seen between retinopathy and nephropathy.

Macrovascular-Cardiovascular Complication s: Risk factors for cardiovascular disease in type 1 diabetes include diabetic nephropathy, diabetic autonomic neuropathy, dyslipedemia, and hypertension. Exact pathogenesis of this complication is not understood. Coronary artery disease pathology may be the result of an interaction from insulin resistance, genetic factors, cytokines and inflammatory biomarkers(white blood cell count) and measures of oxidative stress(e-selectin) interrelationships (Costacou et al., 2005).

Peripheral Vascular Disease: This complication results from atherosclerotic lesions or increased inflammatory activity leading to lumen narrowing causing either stenosis or

thrombus formation (Klabunde, 2007) and is frequently referred to as lower limb arterial disease (LEAD). Increased resistance can lead to reduction in blood flow and hence a decrease in distal perfusion pressure. Vessels most affected include the external iliac and superficial femoral arteries (Klabunde et al., 2007).

Peripheral Neuropathy: Neuropathies are common complications seen in approximately 50% of patients with type 1 diabetes. They are heterogenous and classed as either focal or diffuse. The most common neuropathies are the autonomic neuropathies and chronic sensorimotor distal symmetric polyneuropathy (**DPN**) (Boulton et al., 2005). The American Diabetes Association (ADA) confers importance to the early recognition and treatment of the neuropathies for the following reasons: 1) *Nondiabetic neuropathies may be present in patients with diabetes, 2) A number of treatment options exist for symptomatic diabetic neuropathy, 3) Up to 50% of DPN may be asymptomatic, and patients are at risk of insensate injury to their feet, 4) Autonomic neuropathy may involve every system within the body , and 5)Autonomic neuropathy causes substantial morbidity and increased mortality, particularly if cardiovascular neuropathy **(CAN)** is present* (Boulton et al., 2005).

Sensory neuropathies can be either acute or chronic. **Acute sensory neuropathies** , also referred to as "insulin neuritis" are rare and found to follow prolonged periods of poor glycemic control or periods where there have been sudden changes to the glycemic control. In contrast **chronic sensiomotor DPN** is the most common presentation and is seen in approximately 50% of all diabetics. Clinical symptoms include burning pain, deep aching pain and stabbing sensations usually of the lower limbs. Typically these symptoms are worse at night. There is sensory loss of vibration, pressure, pain and absent ankle reflexes on clinical examination. Screening tests for DPN for advanced abnormality of large nerve fibers includes

vibratory perception tests, proprioception testing and light touch, whereas when clinically testing for small nerve fiber derangement assessment is completed by pinprick and temperature testing (Maser et al., 1991). In the Pittsburgh Epidemiology of Diabetes Complications Study after standard neurological assessment by a trained internist, **distal s ymmetric polyneuropathy (DSP)** was present in 34% of the cohort, 18% was noted in the 18 to 29 year age group while 58% was present in the cohort who were age 30 years or more(Maser et al., 1990). Further review, after 30 years of follow-up of the 1950-1980 Pittsburgh Epidemiology of Diabetes Complications Study cohort, showed a significant temporal decline for autonomic neuropathy at 20 years and a non-significant smaller decline at 25 years (Pambianco et al., 2006). On the other hand there was a decline for both time points at 20 and 25 years for **confirmed distal symetric al polyneuropathy (CDSP**). Independent predictors of **DSP** were **hypertension** status, macrovascular disease, nephropathy and retinopathy (Maser et al., 1990) and **glycemic control** and **duration** (Pambianco et al., 2006). **Focal and multifocal neuropathies result** from neuropathic damage to the ulnar, radial, and common peroneal nerves and are sudden in onset. The presence of **diabetic autonomic neuropathy** (**DAN**) results in significant morbidity. Subsequent mortality can also be seen as well. Clinical presentations of DAN include orthostatic hypotension, erectile dysfunction, gastroparesis, exercise intolerance, resting tachycardia, constipation, impaired neurovascular function and hypoglycemic autonomic failure (Boulton et al., 2005). Review, after 30 years of follow-up of the 1950-1980 Pittsburgh Epidemiology of Diabetes Complications Study cohort, showed a significant temporal decline for autonomic neuropathy at 20 years and a non-significant smaller decline at 25 years (Pambianco et al., 2006). **Cardiovascular autonomic neuropathy (CAN)** is probably the most widely researched of the autonomic neuropathies and considered

the most important because of associated adverse cardiovascular events. CAN has been linked with a poor prognosis due to sudden cardiac death and nephropathy (Arildsen OM, 2000). Arldsen et al randomly drew a gender and age stratified sample of 120 diabetics between the ages of 40 and 75 to test autonomic nervous system function. **E/I ratios** were used as determining autonomic function. Values for E/I ratios >1+exp(-1.12-0.0198 x age(years)) were regarded as normal. CAN prevalence for the type 1 diabetic sample was 38% (95% CI=26-50%). The E/I ratio was found reduced in advanced age, longer duration of diabetes, higher fasting glucose, female gender, and higher triglycerides. There was also a significant association found between urinary albumin excretion and CAN, and that significant reduction in autonomic function predicted future cardiovascular events (Arildsen, 2000). Maser et al (Maser, Mitchell, Vinik, & Freeman, 2003) support an increased risk between CAN and increased risk of mortality (Maser et al., 2003). Following a meta- analysis of 15 studies, results were consistent and strong showing CAN association and increased risk of mortality. Associations were stronger if CAN was defined on the basis of two or more abnormalities (Maser et al., 2003). This association confirmed that those diabetics expressing CAN should be under close surveillance for development of cardiovascular events. Maquire et al (Maguire et al., 2007) followed adolescents with T1D who were assessed for autonomic neuropathy from 1990 to 1993. This study was an attempt to clarify the importance of asymptomatic CAN abnormalities using pupil size, a marker of early autonomic neuropathy, and presence of microalbuminuria and retinopathy 12 years later. After adjusting for glycemic control, the predictive relationship persisted (Maguire et al., 2007). Orchard et al (Orchard, Lloyd, Maser, & Kuller, 1996) also confirmed that those with T1D and DAN have a greater increased risk of mortality related to a specific cardiac etiology. DAN was assessed by E/I ratios obtained in a

two year interval on an incident cohort of type 1 diabetics from the Pittsburgh Epidemiology of Diabetes Complications Study. **Duration of diabetes** and **glycemic control (HbA1)** was found to be the main predictor of DAN. Clearly DAN was associated with an increase in mortality; however this was largely explained by associations with nephropathy and increased cardiovascular risk factors, namely hypertension (Orchard et al., 1996).

Epidemiology of Type 1 Diabetes: Within the United States, the most reliable estimates of type 1 diabetes incidence for youth are the result of three registries that include; the Allegheny County Registry (1985-1994), the Philadelphia Registry (1985-1999) and the Colorado IDDM Study (1978-2004). From 1965 to 1985, the Allegheny County rate was stable. The rate increased in the years 1990-1994, among non-white adolescents(IM Libman et al., 1998). After review of 257 cases identified for the 1990-1994 period, the standardized incidence rate was 16.7/100,000 (95% C.I. 14.7-18.8). This was similar to the incidence rate generated for 1985-1989 of 17.1/100,000(IM Libman et al., 1998). There was a higher rate among males (17.2/100,000) than females (14.4/100,000) (Libman IM, 1998) and, for the first time the incidence rate was higher in non-whites [17.6/100,000] than whites [16.5/100,000] (Libman IM, 1998). The incidence for the older age group (15-19 years) was higher in non-whites [30.4/100,000(95% C.I. 18.3-47.4)] than whites for that same age category [11.2/100,000(95% C.I. 7.6-15.9)] and accounted for almost a three fold increase (Libman IM, 1998). The rate effect was seen in both the males and females. The white population maintained a higher incidence in the younger age group (0-14 years) however. Please refer to Table 2.2.

Table 2.2 Type 1 Diabetes Incidence Rate for Allegheny County by Race/Age Group (Libman IM, 1998)

Age Group (years)	Incidence in Whites Rate/100,000 (95% C.I).	Incidence in Blacks Rate/100,000 (95% C.I).
0-4	9.5(6.6-13.4)	5.2(1.4-13.4)
5-9	20.7(16.2-26.3)	13.8(6.3-26.1)
10-14	24.9(19.9-31.3)	23.6(12.9-39.7)

Similar findings were reported by the Philadelphia Registry showing a stable rate for the non-Hispanic whites and Hispanics from 1985-1999 with an increase in the incidence for black children. The Colorado Study Group found an increasing incidence of type 1 diabetes from 1978-2004 in 0-17 year olds (Vehik et al., 2007). The incidence rate for period 1 (1978-1988) was 14.8/100,000(95% C.I.14.0-15.6) while period 2 (2002-2004) showed a much higher rate of 23.9/100,000(95% C.I 22.2-25.6)(Vehik et al., 2007).

To monitor incidence patterns of type 1 diabetes in children ≤14 years of age, the World Health Organization (WHO) established the Multinational Project for Childhood Diabetes (DiaMond) Project in 1990. This project also, was to determine genetic risk factors associated with complications and mortality of diabetes (Podar et al., 2000). Incidence rates were generated from 114 populations in 112 centers in 57 countries. Of 84 million children, 43,013 were diagnosed with T1D (DIAMONDProjectGroup, 2006). Within the various populations, the overall age-adjusted incidence rates varied. The lowest incidence was found in China and Venezuela with 0.1/100,000 while the highest reported was for Finland at 40.9/100,000. Asian population were for the most part found to have a very low incidence (<1/100,000). The highest incidence rates were found in the North American and European

populations, 11-25/100,000 and 4-41/100,000 respectively (DIAMONDProjectGroup, 2006). There were no marked age specific incidence differences between genders. There were however found incidence rate differences between age groups, with increasing incidence found with increasing age. Calculated mean annual incidence increase was 2.8% (95% C.I. 2.4-8.6). Confirmed from the DIAMOND Project is that the risk of type 1 diabetes has been increasing since the 1950's and there is no current indication that this trend is not continuing (DIAMONDProjectGroup, 2006).

A diagnosis of **cardiovascular disease** was reported in approximately 37.2% of all persons with diabetes 35 years or older in the year 2000 Ischemic heart disease prevalence for those with diabetes was approximately 14 times the rate of those without diabetes for the 18-44 age group, three times higher in the 45-64 age group and almost twice as high in those 65 years or older (Engelau, 2004). Absolute rates of cardiovascular disease are higher in men than women, however the relative risk of cardiovascular disease is higher in women (2-4) than men (1.5-2.5) (Engelau, 2004).

In persons age 20 to 64 years of age, **retinopathy** is the leading cause of blindness. This complication of diabetes accounts for 12,000 to 24,000 new cases of blindness each year within the United States.

Nephropathy attributed to diabetes accounts for 40% of all new cases per year of end-stage renal disease. Those with diabetes also account for the largest percentage of patients receiving dialysis and transplantation per year. **Peripheral arterial disease** is diagnosed in 8.1% of those with diabetes as opposed to 4% in the general population. **Peripheral neuropathy:** Those with diabetes have 2-3 times the prevalence of **peripheral neuropathy** than those without diabetes. Prevalence for Diabetic Autonomic Neuropathy (DAN) can be as

high as 90% but reported prevalence depends on population examined, clinical tests conducted and type and duration of the disease. Risk factors include age, duration of diabetes, and long term glycemic control. DAN is also seen concurrently with hypertension and dyslipidemias.

In addition, there is a global geographic variation seen with microvascular and macrovascular complications. The DiaComp study, a sub-study of the WHO DiaMond Study, was a multinational (17 countries) cross-sectional analysis of complications seen in T1D (Walsh MG, 2005). This group reported more geographic variability than did the EURODIAB IDDM Complications Study. Duration of diabetes for the DiaComp Study was catorgorized into one of two groups: 1) short duration of T1D (5-14 years), or 2) long duration of T1D (15-24 years). There were high rates of microalbuminuria and renal disease. Neuropathy was high in the eastern European countries as well for the short duration group. Israel and Finland showed high rates of neuropathy for both short and long duration groups. EURODIAB did concur with the higher rates seen in eastern Europe for those diabetics with <14 years duration however (Walsh, Zgibor, Songer, Borch-Johnsen, & Orchard, 2005).

Mortality due to diabetes: Diabetes is the fifth leading cause of death within the United States (Association, 2003). Deaths due to cardiovascular disease account for 65% of all deaths in those persons with diabetes. A population based study in Rochester, Minnesota (all types of diabetes) reported a decrease in cardiovascular mortality between 1970 and 1994 by 13.8%. However this did not match the decline in cardiovascular deaths in those without diabetes which was a decline of 21.4 %(Thomas et al., 2008). Pambianco et al (Pambianco et al., 2006)reported a decreasing trend by diagnoses year for mortality, neuropathy and renal failure from the Pittsburgh Epidemiology of Diabetes Complications Study cohort. Less

favorable trends for cardiovascular, overt nephropathy and proliferative retionopathy complications were seen after 30 years of follow-up (Pambianco et al., 2006).

It is predicted that by the year 2050 within the United States, there will be 48.3 million people with diabetes. From 2005 to 2050, total prevalence is expected to more than double from 5.62 to 12.00% (Narayan, Boyle, Geiss, Saaddine, & Thompson, 2006). Both sexes are projected increases with men up by 174% and women by 220%. Among non-Hispanic whites, diabetes prevalence is expected to increase by 99% and for non-Hispanic blacks 107%. The prevalence increase for Hispanics is expected to increase by 127% and 158% for all other races (Narayan et al., 2006). In 2002, the health care costs for people with diabetes were more than double that for those without diabetes (Association, 2003). It is estimated that more than $1 in $10 spent on health care services is the result of diabetes (Association, 2003). Over $160 billion was spent in 2002 to provide health care services for those with diabetes. Estimates for health care expenditures for neurological disease care associated with diabetes totaled $2,748 million, while those associated with peripheral vascular disease were $1,121 million, cardiovascular disease $17,626 million, renal $1,879 million and ophthalmic complications $422 million (Association, 2003). Therefore, the impact of diabetes mellitus is not only to the individual but to society as well and because of the increasing prevalence of this disease the cost burden to society remains.

2.1.8 Pathophysiology of Erectile Dysfunction and Diabetes

There is a multifactorial etiology to ED seen in males with diabetes. Comorbidities associated with diabetes, end-organ damage due to hyperglycemia and side-effects of medications used to treat concurrent diseases all contribute to the etiology of ED in diabetes. In addition, these

biochemical mechanisms contribute to the etiology of ED in males with diabetes as well. They are as follows: 1) elevated advanced glycation end-products (AGE's), 2) impaired nitric oxide (NO) synthesis, 3) increased levels of oxygen free radicals, 4) impaired/decreased cyclic guanosine monophosphate (cGMP)-dependent kinase-1(PKG-1), 5) increased endothelinB (ETB)receptor binding sites and ultrastructual changes, 6) upregulated RhoA/Rhokinase pathway and 7) NO dependent selective nitrergic nerve degeneration. The mediating pathway of each of these mechanisms will also be briefly discussed in relation to the development of ED.

Elevated Advanced Glycation End –products : AGE's are produced secondary to hyperglycemia in people with diabetes. These are the biochemical end products of non-enzymatic reactions between glucose and lipids, nucleic acids or proteins that have undergone further irreversible chemical modifications. Vascular thickening, decreased elasticity, endothelial dysfunction and atherosclerosis result when AGE's form covalent bonds with vascular collagen. These accumulate in the aging and diabetic tissue, forming at an accelerated rate with glucose elevation. AGE's can be found in elevated levels in the corpus cavernosal tissue of diabetic rats and humans. These elevations then result in impaired smooth muscle relaxation in the corpus cavernosum. The pathophysiological pathway has been posited that AGE's contribute to ED by generating oxygen free radicals , which then cause oxidative cell damage and impaired NO synthesis, further causing a decrease in cGMP and in turn resulting in impaired smooth muscle relaxation.(Bivalacqua et al., 2005; Cartledge, Eardley, & Morrison, 2001; Moore & Wang, 2006; Yamanaka et al., 2003).

Nitric Oxide(NO): The endothelium of the arteries of the penis produce NO. NO is responsible for mediating relaxation of the corpus cavernosum through the formation of cGMP.

Corpus cavernosum relaxation is primarily the result of nNOS (neuronal nitric oxide synthase) activity within the nitregenic neurons of the penis. Reduced amounts of nNOS have been shown in diabetic rats. This decrease in NOS activity has also been shown in human penile tissue in those with diabetes and ED (Saenz de Tejada et al., 2005; Tuncayengin et al., 2003; Vernet et al., 1995). It has be hypothesized that diabetes impairs guanylyl cyclase activity causing reductions in cGMP production. Effector cGMP participate in the production of diabetic ED. Thus in summary, NO and the effector molecule cGMP contribute to the development of diabetic induced ED(Moore & Wang, 2006).

Protein Kinase -1(PKG-1) Cavernosal smooth muscle relaxation is caused by cGMP primarily though PKG-1. PKG-1 alters intracellular calcium levels and opens the calcium dependent potassium channels causing hyperpolarization of the smooth muscle cells. Decreased levels of PKG-1 were shown in corporal cavernosal smooth muscle cells of both diabetic rat and rabbit animal models. Decreases in PKG-1 is thought to augment diabetic ED by diminishing the cGMP intracellular activity pathway(Chang et al., 2004; Moore & Wang, 2006; Saenz de Tejada et al., 2005).

Enothelin B Receptor binding sites(ETB) and Ultrastructual Changes: Endothelin (ET) is a known constrictor of non-vascular and vascular smooth muscle. As a result of ET and its receptors, there is evidence to suggest that ED in diabetes is caused by an imbalance toward increased penile vasoconstriction. There are three isopeptides to ET (1, 2, 3) and two G protein coupled receptors (ETA and ETB). .Produced by the vascular endothelium and a potent penile vasoconstrictor is ET-1. It is ET-1 that is elevated in the plasma of diabetics.

ETA receptors mediate vasoconstriction and cellular proliferation and are located on smooth muscle. ETB receptors are found on the vascular endothelium where their primary

function is to mediate vasoconstriction through NO and prostocyclin production (Bivalacqua, Usta, Champion, Kadowitz, & Hellstrom, 2003; Moore & Wang, 2006; Saenz de Tejada et al., 2005; Sullivan et al., 1997). ETB receptors mediate vasoconstriction in canine coronary arteries and human mammary arteries (Teerlink, Breu, Sprecher, Clozel, & Clozel, 1994). It is hypothesized that ETB receptors may cause an imbalance that affects a tendency towards penile vasoconstriction. It is also hypothesized that ETB receptors are linked to early ultrastructual changes of atherosclerotic lesions in diabetics and venous occlusive penile function (Sullivan et al., 1997).

RhoA/Rho-kinase: ET-1 induced vasoconstriction is linked to the RhoA/Rho-kinase pathway. It is through the activation of this pathway that NOS is suppressed and the production of NO is decreased. It is hypothesized that the RhoA/Rho-kinase pathway mediates ED by decreasing NO production in penile tissue(Moore & Wang, 2006; Rees, Ziessen, Ralph, & Kell, 2002; Saenz de Tejada et al., 2005).

Neuropathy: Diabetics with ED have abnormal nerve conduction.more frequently than diabetics without ED. It is also noted that diabetics with neuropathic ED also have somatic and autonomic neuropathies, hence suggesting that neuropathy contributes to diabetic ED.

2.1.9 Epidemiology of Erectile Dysfunction and Diabetes

The ***prevalence*** of ED and diabetes has been reported to be anywhere from 20% to 71% (Feldman et al., 2000; Klein, Klein, Lee, Moss, & Cruickshanks, 1996; Nathan, Singer, Godine, & Perlmuter, 1986). The large discrepancy reported in the prevalence estimates is affected by the sensitivity and specificity of methods used to assess ED. Several of the studies reported statistics based on record reviews while others reported face to face assessments,

where ED is under-reported. Also studies did not control for type of diabetes, severity of ED, duration of disease and glycemic control (Penson, Latini et al., 2003). Unlike the above, our EDC study only completed analysis on males with T1D and the analysis of the EDC data for males with ED controlled for duration and glycemic control.

A 20% prevalence rate was reported by Klein et al (Klein et al., 1996) from a population based cohort study in southern Wisconsin. These estimates were self-reported by 365 males greater than 21 years of age, who were less than 30 years of age at diagnosis, had 10 or more years of diabetes and were on insulin therapy. ED was associated with a history of peripheral neuropathy, amputation, cardiovascular disease a higher HbA1, higher BMI, use of anti-hypertensive medications, severe retinopathy and longer diabetes duration. Prevalence of ED increased from 1.1% in the 21-30 year age group to 47% in those older than 43 years (Klein et al., 1996).

Fedele et al (Fedele et al., 2001) reported a prevalence of 26% in a sample of 1, 383 T1D males from 178 Italian diabetes centers. Findings as above were confirmed and an additional significant positive association for smoking was found for those with ED (Fedele et al., 2001). Klein et al (Klein et al., 2005) also completed a 10 year incidence of self-reported ED in males with long term type 1 diabetes from a study population from 11 counties in southern Wisconsin (Klein et al., 2005). From a registry, 10, 135 persons with diabetes were identified of which 1210 were identified as having diabetes prior to age 30. Only males who participated in the 10, 14 and 21 year examinations and who were 21 years or older were eligible to participate because ED was first obtained at the 10 year examination. These totaled 365. After controlling for age, males with ED at the 10 year examination time were more likely to die with a reported hazard ratio of 2.7(95% CI 1.5, 5) than males without ED. Males with

25 or more years duration of diabetes, were 2.4 times (95% CI 1.1, 5.1) more likely to self report ED than males with 11-14 years diabetes duration. This relationship was no longer found statistically significant after controlling for age.

Overall 10 year incidence of ED increased from 10.2% in males between the ages of 21 and 29 to 48.6% in males older than 40 years ($p<.001$). Total serum cholesterol, but not HDL was related to incidence of ED. However, ED was not statistically significantly related to higher HbA1's. If hypertension was present, the male was three times as likely to have ED. Current use of anti-hypertensive medications was not statistically significant in association of those with ED and those without. Age, hypertensive status and smoking were statistically associated with incident ED. Persons married were more likely to report ED but not statistically significant after controlling for age. However, ED was not associated with income, education or work status. Long term complications associated with ED and statistically significantly related to ED included neuropathy, lower extremity pain on walking, presence of more severe retinopathy at baseline and loss of sensation. Those with proliferative retinopathy were 2.1 times more likely to report incident ED (Klein et al., 2005).

From our review of the previous prevalence studies, and in summary, prevalence was noted to be anywhere from 20% to 71%. Demographic risk factors identified were increasing age, marital status, income, and education (Klein et al., 1996) while the biologic risk factors identified were duration of diabetes greater than 10 years, HbA1c, complications (peripheral neuropathy, peripheral vascular disease, cardiovascular disease , and retinopathy), hypertension, and total cholesterol (Fedele, 1998; Klein et al., 1996) and anti-hypertensive medication. Lifestyle behavioral risk factors identified were smoking(Fedele, 1998).

Demographic risk factors associated with incident studies included demographic (age, marital status) and biological (duration of diabetes, complications [neuropathy, severe retinopathy], total serum cholesterol but not High Density Lipoprotein, hypertension.) and lifestyle behavioral risk factors (smoking, alcohol)(Fedele et al., 2001; Klein et al., 2005). Demographic risk factors common to both previous prevalence studies and incidence studies included age, and marital status. The biological risk factors included glycemic control, duration of diabetes, complications (peripheral neuropathy, cardiovascular disease, severe retinopathy, and peripheral vascular disease), blood pressure, weight, and total Cholesterol(Fedele et al., 2001; Klein et al., 1996). These risk factors have all been assessed by the EDC Study and were included as variables in this study. In addition our study assessed additional biologic factors (E/I ratios) that were not previously reported in the literature.

In addition to the demographic, biological and lifestyle behavioral risk factors, our study assessed depressive symptomatology and quality of life's association with the development of ED. The following describes what has been reported in the literature.

2.1.10 Psychosocial Risk Factors

Quality of Life and Depression

Risk factors for males with ED include depression, anxiety, and a negative impact on relationships. These compounded with diabetes can have a substantial effect on the quality of life (QOL). The association between poor quality of life and ED has been established, however, ED is infrequently addressed by diabetes specialists and primary care physicians (DeBerardis et al., 2005; Kalter-Leibovici et al., 2005). Because of the psychosocial implications of ED, males with ED do not actively seek treatment. In a survey of 500 males

over the age of 50 who visited a urologist for urologic issues other than ED, 44% or 218 males had ED. These males with ED did not seek professional help for ED because they were embarrassed or viewed ED to be a symptom of aging (Baldwin, Ginsberg & Hawkins, 2003). Findings from the National Health and Social Life Survey reported that despite the diminished quality of life experienced by males with ED, only 1 in 10 reports and seek medical treatment for ED (Laumann et al., 1999). Findings from the Exploratory Comprehensive Evaluation of Erectile Dysfunction(ExCEED) (Penson, Wallace et al., 2003) study not only confirmed this disease specific negative quality of life association, but also confirmed that males with ED and diabetes report worse erectile dysfunction than males with ED and no diabetes. This study was an observational longitudinal registry study that examined males with ED who sought urologic care for sexual dysfunction. Males with ED and diabetes (cohort definition for diabetes both T1D and T2D) reported more severe sexual dysfunction than those males without diabetes, and, worse disease specific health related quality of life (HRQOL). Functional status and disease specific HRQOL were measured at 3, 6 and 12 months after baseline in both the non-diabetic and diabetic male groups. Males with diabetes and ED responded differently over time. Six months after baseline, the males with diabetes showed marked improvement in HRQOL but this trend did not continue as 1 year after baseline the males with diabetes and ED reported worse HRQOL than those without diabetes and ED. In addition, males with ED and diabetes initially respond well to treatment, but the treatment effect is not sustained over time (Penson, Wallace et al., 2003) which also may have a negative impact on QOL.

These studies focused on the psychosocial impact of ED, not on analyzing them as potential predictors of ED. Our study analyzed depressive symptomatology and quality of life as risk factors for ED.

The association with depression and ED has been previously addressed in the preceding sections. For a summary of the above mentioned research studies, please refer to APPENDIX A:Summary of ED Studies.

2.1.11 Behavioral and Cognitive Factors

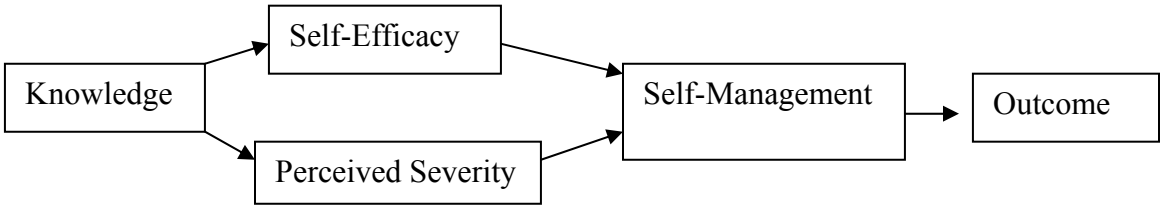
Because diabetes mellitus requires self-management behaviors for survival, behavioral and cognitive factors were important to examine in this study. Behavioral theory helps to direct the hypothesis and measures. The Conceptual Framework that guided our analyses was the Social Cognitive Theory.

Social Cognitive Theory (SCT) posits that individuals are governed by their own self system. Within this, there is a self-referent mechanism to provide value and meaning on environmental events. These events then serve a regulation function to shape how the individual thinks, feels and acts (Bandura 1990). Therefore, seen as cognitive self-evaluations, these exert influence on such behaviors as goal attainment, the amount of energy expended toward attaining these goals, and their likelihood of attaining this level of behavioral performance. SCT has a set core of determinants, a mechanism through which those determinants work and the most effective ways of translating ***knowledge*** into effective health care practice (Bandura, 1988; Bandura & Bussey, 2004). Through this cognitive self evaluation, the individual is able to not only evaluate their experiences but also develop their sense of *self-belief.* An individual's behaviors are mediated by their own self-beliefs and, an individual is able to attain higher self -performance if functioning within high levels of positive self-belief accompanied by a higher sense of control. To understand and intervene in health behavior, Mishel and Bandura formulated a number of SCT constructs (Bandura & Bussey,

2004). Two of the SCT constructs used in health behavior intervention models include outcome expectancy and ***self-efficacy***. An individual's estimate that a given behavior will lead to a certain outcome is the definition for outcome expectancy and therefore leads the individual to behave in a manner that maximize positive outcomes and minimize negative ones. Bandura identified the most important determinant for behavioral change to be *self-efficacy* and this is the construct most often applied to research of self-management behaviors in chronic disease. Self-efficacy is the *individual's belief about ability to organize and execute the course of action necessary to attain a given outcome.* Bandura placed more importance to this construct because he believed that self-efficacy affects how much effort is invested in and what level of performance is attained in a given health related task. Self- efficacy will influence selection, course of action, individual effort, time and perseverance spent despite barriers presented to attain the goal. Individuals are more likely to take on a task if they believe they can succeed. If one repeatedly completes a health related task successfully, the success reinforces the behavior which in turn promotes a behavioral change (Bandura, 1988; Glanz, Rimer, & Lewis, 2002). Self-efficacy affects health behavior directionally and by influencing other determinants. Bandura lists four sources that affect self- efficacy. The first source is mastery and considered to be the most important source. Simply put, success *will raise self-efficacy where failure will lower it.* The second is modeling. By this process, a comparison is made between the person and a peer. The third is social persuasion. Positive persuasions by health care professionals increase self-efficacy. And finally the fourth and last sources are physiologic factors. A person's perception of normal physiologic responses to stress can alter their level of self-efficacy. How an individual cognitively appraises the information, is determined by the impact of the efficacy information from these four sources. Several studies have reported that higher

self efficacy is associated with higher levels of self-management (Anderson et al., 1995; Glasgow & Anderson, 1995; Hurley & Shea, 1992; Johnson-Brooks, Lewis, & Garg, 2002) in people with diabetes**.** A conceptualized model with the role of self-efficacy and its relationship to self–management behavior and outcome is depicted through the following Figure 2.1

Figure 2.1 Application of the SCT



According to the literature, enhancing diabetes reself-management (diabetes treatment regimen) leading to more positive outcomes (metabolic control and prevention of complications). Successful management of diabetes relies on the individual with diabetes' ability to repeatedly and successfully complete tasks to control symptoms and delay or prevent long term complications. An additional self-belief that may contribute to this behavior is perceived severity (Health Belief Model) (Becker, 1974; Glanz et al., 2002). Understanding self-management behaviors and health beliefs (self-efficacy and perceived severity) may help the clinician to recognize potential barriers to adherence. There have been several studies concerning self-efficacy and diabetes adherence (Johnson-Brooks et al., 2002; Kneckt, Syrjala, Laukkanen, & Knuuttila, 1999). The gap exists in the research dealing with self-management behaviors, health beliefs and knowledge, in males with ED and Diabetes.

2.1.12 Treatment of Erectile Dysfunction

Several treatment options are available to males with ED, prescription of which is based on the underlying cause and over–all health of the male. Non-pharmaceutical effective measures are changes in lifestyle that include: 1) regular exercise to decrease weight, relieve stress, depression or anxiety, improve muscle tone, increase energy levels and lower blood pressure, and, 2) smoking cessation. There are also vacuum erection devices that can be effective, elective penile prosthetic surgery or penile revascularization surgery. There are pharmaceutical agents approved by the FDA for use in ED that are the Phosphodiesterase Inhibitors which inhibit PDE5, the primary agent in cavernosal tissue responsible for degradation of cGMP. By inhibiting PDE5, prolonged levels of cGMP can be maintained with improved smooth muscle relaxation.(Saenz de Tejada et al., 2005).

2.1.13 Treatment of Erectile Dysfunction in Diabetes

Diabetic ED treatment is multimodal. Medications used to treat comorbidities of diabetes should be chosen that have the least adverse effect on erectile function. Males with diabetes with cardiovascular comorbidites need assessment prior to the initiation of therapy to treat ED. The Second Princeton Consensus Conference delineated three risk levels based on cardiovascular status and risk in the male with diabetes to determine treatment protocols. Those in the high risk group need to achieve cardiovascular stabilization prior to receiving treatment. It is recommended that the intermediate risk group receive assessment by a cardiologist prior to the initiation of treatment and the low risk group considered for all first line therapies used in ED treatment (Kostis et al., 2005). There are presently 5 treatment

options available for males with diabetes and ED. Phosphodiesterase Inhibitors inhibit PDE5 which is the primary agent in cavernosal tissue responsible for degradation of cGMP. By inhibiting PDE5, prolonged levels of cGMP can be maintained with improved smooth muscle relaxation (Saenz de Tejada et al., 2005). Sildenafil is a PDE5 inhibitor and is frequently prescribed. In a study comparing Sildenafil versus placebo in males with type 1 diabetes and ED, those on Sildenafil reported improvement in ability to achieve and maintain erection (Stuckey et al., 2003). Similar results were obtained in a study by Rendell et al in which 61% of the Sildenafil treated versus 22% of the placebo reported at least one successful intercourse attempt (Rendell, Rajfer, Wicker, & Smith, 1999). Overall the PDE5 inhibitory drugs are well tolerated by males with diabetes and ED. Global efficacy of maximum dose PDE5 inhibitors has been reported in the range of 65-72% (Boulton et al., 2005; Saenz de Tejada et al., 2005) .

Vacuum erection devices are also an option for males with diabetes and ED. This is a cyclindrical chamber device with a pump on one end and an opening on the other end. After lubrication of the penis, the device is placed over the penis, a tight seal is formed at the base of the penis,and either manually or by battery the pump is activated. When the penis has reached sufficient engorgement for an erection, a tension ring is placed at the base of the penis thus trapping blood in the corporal bodies and an erection is maintained. There is a 30 minute limit to the constriction ring being in place. This device is contraindicated for those using anticoagulants, or having a history of bleeding disorders. Patient satisfaction is limited with the use of this device.(Moore & Wang, 2006; Price et al., 1991; Saenz de Tejada et al., 2005) (Sidi, Becher, Zhang, & Lewis, 1990).

A third option is the use of intraurethral suppositories. Alprostadil (prostaglandin E) is absorbed by the urethra causing vasodilatation and relaxation of the smooth muscle. Other

treatment options available include penile prosthesis, used when oral treatment is contraindicated or fails, and intracavernosal injection. Research for the treatment of ED in diabetes continues 1) in the identification of the underlying cause, and, 2) gene therapy with neurotrophic factors.

In summary, this review of the literature has discussed: 1) the pathophysiology of ED, 2) the pathophysiology of ED as it relates to or is altered by diabetes, 3) T1D, 4) epidemiology of T1D, 5) epidemiology of ED, 6) the epidemiology of ED and diabetes and, 7) treatment options for males with diabetes and ED.

3.0 RESEARCH METHODOLOGY

The present study involved a secondary data analysis of data collected from male participants of the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study (1986-2007). The EDC was an NIH (DK34818) funded study designed to address the following three research questions; *1) Why do insulin dependent diabetic patients develop complications? 2) What factors relate to the type and combination of complications that individual IDDM patients suffer*? and, *3) What factors relate to the severity of complications*?

There were two major components to this study. The first was a baseline (prevalence) cross sectional analysis of the study cohort designed to determine the prevalence and interrelationships of macrovascular and microvascular complications. The second was a prospective longitudinal study that documented the incidence and natural history of new disease in participants free from clinical disease at baseline by evaluating interrelationships between risk factors in the subsequent development and progression of diabetes complications. The major complications of interest included cardiovascular disease, peripheral vascular disease, retinopathy, nephropathy and neuropathy.

Erectile Dysfunction (ED) was included as a clinical symptom of symptomatic autonomic neuropathy. However, at the time of the study's inception, ED was not included as a major complication of interest. Since this type of research plan involves post-hoc analysis, a limitation that is sometimes encountered is that there can be no planned measure for the variable of interest, and therefore it is sometimes necessary to create a variable within the original dataset that matches the variable of interest. Because ED, the present variable of interest, was included within the parent study design, this was not seen as a limitation for this analysis.

The proposed analysis of the male participant's data from the parent study had the following primary objectives: 1) to determine both the prevalence and incidence of ED in the EDC sample; 2) to identify risk factors for development of ED; and 3) to determine the natural history of ED, specifically if ED development occurred at a particular stage of neuropathic disease. The secondary objective was to identify longitudinal self-management behaviors of males with ED enrolled in the EDC related to their self-efficacy, perceptions of severity of complications of diabetes and diabetes knowledge.

3.1 SAMPLE, SETTING, AND PROCEDURE

The participant pool for the parent study was obtained through the use of the Children's Hospital of Pittsburgh Registry. This registry consisted of all insulin dependent diabetes mellitus patients seen at Children's Hospital of Pittsburgh from January 1, 1950 to May 31, 1980 and formed the sampling frame for inclusion in the EDC. Subjects had to meet the following criteria: 1) onset of insulin dependent diabetes mellitus at age 17 years or less; 2)

insulin therapy prescribed at discharge; 3) an initial diagnosis, or being seen within one year following diagnosis at Children's Hospital of Pittsburgh; and 4) residence within 100 miles of Pittsburgh or 2.5 hours of driving distance from Pittsburgh.

There were 1124 patients identified from the registry that met the inclusion criteria. Of these, 145 had died before recruitment, leaving 979 subjects. Attempts were made to contact all 979 by mail and phone. Of the 979 eligible patients, 788 (80%) agreed to participate. About two thirds (n=658, 67%) provided full participation and 130 (13%) completed only questionnaires. Those who agreed to fully participate were seen for baseline examinations between 1986 and 1988.

Males composed 51% (n=333) of the total sample. Of the 333 males, 331 were Caucasian and 2 were African American. Age range for the males at study entry was from 8.47 years to 47.43 years with a mean age of 27.53±7.78 years and a median age of 27.27 years. The duration of diabetes varied: 13 % (n=44) had diabetes duration less than 10 years, 40 % (n=136) had diabetes duration between 10 and 19 years, 35% (n=117) of the participants had diabetes duration between 20 and 29 years and, 11 % (n=36) of the participants had diabetes duration 30 years or more. Overall mean and median for duration of diabetes was 19.6 years (± 7.5 years) and 18.96 years respectively. Table 3.1 illustrates the distribution of the age of the male participants by duration of diabetes. Hemoglobin A1 mean at baseline was 8.7% ± 1.45%(normal range 4.7%-6.8 %). Twenty-two percent (n=75) of the males actively smoked at baseline, while 57 %(n=190) admitted to ever smoking 100 cigarettes in their lifetime. Fifty-three percent (n=175) were not married. Table 3.2 illustrates the overall characteristics of the male sample at baseline.

Table 3.1 Age by Duration of Diabetes in Male EDC Participants at Baseline (1986-1988)

	Duration	**of**	**Diabetes**	**(years)**	
	<10 years	0-19	20-29	>30	Total
Age (years)					
<18 n=32	23	9			32
18 to 25 n=104	20	67	17		104
25 to 30 n=70	1	47	22		70
30 to 35 n=63	0	13	43	7	63
35 to 40 n=44	0	0	31	13	44
>40 n=20	0	0	4	16	20
Total	44	136	117	36	333

Table 3.2 Characteristics of Males with T1D Enrolled at Baseline (1986-1988) in the EDC

Characteristics	Total n=333
Age (m±sd) years	27.53±7.78 Range: 8.47-47.43
MARITAL STATUS (n,% total) never married married separated divorced widowed not married, living with partner	 175 (52.55) 131 (39.34) 2 (0.6) 18 (5.41) 0 7 (2.10)
LEVEL OF EDUCATION (n,% total) SomeHS/HS graduate Some College Graduate	 118 (39.46) 154 (51.51) 27 (9.03)
INCOME (% total) <$5,000-$15,000 $15,000-$30,000 >$30,000	 26.12 38.05 35.82
HbA1c (m±sd) %	8.74 ±1.45 Range: 5.23-15.16
Age at onset of diabetes (m±sd) years	8.34 ± 4.17
Duration of diabetes (m±sd) years	19.55±7.46 Range: 7.69-37.40
Total Complications	1.18 ± 1.35 Range: 0-5
Coronary Artery Disease (CAD) (n, % total) no yes	 305 (91.59) 28 (8.41)
+Autonomic Neuropathy (AN) (n, % total) no yes 92	 60 (65.22) 32 (34.78)
+Symptomatic Autonomic Neuropathy (SAN) (n, % Total) n=92 no yes	 83 (90.22) 9 (9.78)

Table 3.2 continued

Nephropathy (n, % total) no yes	 238 (71.47) 95 (28.52)
Lower Extremity Arterial Disease (LEAD) (n, % total) no yes	 308(93.05) 23 (6.95)
Retinopathy (n, % total) no yes	 219 (67.18) 107 (32.82)
Cerebral vascular Disease(CBVD) (n, % total) no yes	 331 (99.4) 1 (0.3)
Confirmed Distal Symmetrical Polyneuropathy (CDSP) no yes	 230 (69.27) 102 (30.73)
Distal Symmetrical Polyneuropathy (DSP) no yes	 227 (68.37) 105 (31.63)
Systolic Blood Pressure (m±sd) mmHg	117.49±17.14 Range: 76-234
Diastolic Blood Pressure (m±sd) mmHg	75.52±11.20 Range: 44-118
High Density Lipoprotein (HDL)	48.61 ± 9.73
nonHDL Cholesterol	140.60 ± 44.56
Smoking Ever (n,% total) n=322 no yes	 190(59.01) 132(40.99)
Smoking Now (n.% total) n=125 no yes	 50(40) 75(60)
Total alcohol (Average drinks /wk) N=192	6.17 ± 11.1 Range:0-53
Hypertensive (n,% total) no yes	 268 (80.72) 64 (19.28)
ACE Medication (n, % total) no yes	 307 (96.54) 11 (3.46)

Table 3.2 continued

Blood Pressure Medication (n,% total) no yes	 257 (90.49) 27 (9.51)
Quality Of Life (QOL) (m ± sd)	52.72 ± 12.19 Range: 33-129
Impact (m ± sd) (Domain within QOL instrument)	30.00 ± 6.75 Range: 19-53
Worry (m ± sd) (Domain within QOL instrument)	16.41± 6.42 Range:1-44
Satisfaction (m ± sd) (Domain within QOL instrument)	5.99 ± 1.96 Range: 3-11
Sex Question (m ± sd) (Question within Impact Domain/QOL Instrument)	1.72 ± 1.10 Range: 1-5
BECK Depression Inventory (BDI)(m ± sd)	6.2±6.20 Range:0-32

After scheduling the baseline examination and 2 weeks prior to their examination at the Diabetes Research Center at the University of Pittsburgh, participants were mailed self-report questionnaires that included a medical history, lifestyle questionnaire and containers with detailed instructions for 24 hour urine and overnight specimens collection that were to be brought to the research center the day of the examination. If a participant failed to show for an appointment, contact was made by the research staff and the participant was asked to complete the questionnaires only and return them via the mail (Orchard et al., 1990). Procedures completed once the participant arrived at the research center and according to protocol included: 1) review and verification of self-report questionnaires with research staff; 2) fasting blood draw, insulin and breakfast; 3) clinical examination and procedures for retinopathy, cardiovascular and neurological status; and 4) exit interview with the research physician. Total time participants were present within the research center was approximately 4 hours. Participants were given a stipend for their time and travel. Results of examination and clinical evaluations were sent to the participant's physician for review.

Data were then collected biennially on this cohort, for a period of 10 years (1986-1998). Each cycle (refer to Table 3.3 for actual cycle dates), Cycle 1 through Cycle 6, of exams took place over a 10-year period and included face-to-face clinic visits, physical assessments, laboratory testing and self-report. Collection of data continued after the ten year follow-up with annual surveys and a full examination at 18 years (2004-2007) using the above methods. Data was not ascertained on all enrolled participants at Cycle 7(1998-2000) or Cycle 8/9 (2000- 2002) as these 2 cycles were EDC-sub studies.

Table 3.3 Dates for Cycles 1 through 10, EDC

Cycle 1:	May,1986-November, 1988
Cycle 2:	November, 1988-November, 1990
Cycle 3:	November, 1990-November, 1992
Cycle 4:	November, 1992-November, 1994
Cycle 5:	November, 1994- November, 1996
Cycle 6:	November, 1996-November, 1998
Cycle 7: (EDC substudy if T1D Duration >30yrs)	November, 1998-November, 2000
Cycle 8/9: (EDC substudy for Coronary Artery Calcification study)	November, 2000-November, 2004
Cycle 10:	November, 2004-March, 2007

As per EDC protocol, questions concerning sexual maturity were asked by the examining physician only if thought appropriate to those older than 16 years of age. Because ED is only present in males who have reached an age of sexual maturity, a criterion for participation in the present study was age greater than or equal to age 18 years. Therefore, the age of the participant was an additional criterion to the above set of eligibility criteria in the present study. At baseline of the 333 males enrolled, 32 of those males were below the age of 18 years. In addition to their age, these 32 males statistically differed from the other 301 males in duration of diabetes, weight, height, total cholesterol, high density lipoproteins, low

density lipoproteins, systolic and diastolic blood pressures, waist hip ratios, and BMI. No statistical difference between the samples was found for HbA1, a measure of diabetes control, and triglycerides. In addition, these two samples differed in complications of retinopathy, nephropathy, and neuropathy (CDSP). They did, however, not differ in coronary artery disease or lower extremity arterial disease. Refer to Table 3.4.

Table 3.4 Characteristics of Males Older than 18 years of Age at EDC Baseline (1986-1988) as Compared to Males Younger than 18 years of Age at EDC Baseline

Characteristics	Males older than 18 years (n=301)	Males younger than 18 years (n=32)	p-value
Age (± sd) (years)	28.96 ± 6.69	14.02 ± 2.60	p<.0001
Duration of Diabetes (years)	20.62 ± 7.03	9.51 ± 1.41	p<.0001
Weight (kgms)	71.67 ± 9.81	50.53 ± 14.07	p<.0001
Height (cms)	172.78 ± 6.51	158.98 ± 14.01	p<.0001
Total Cholesterol	193.39 ± 44.62	160.65 ± 26.25	p<.0001
High Density lipoprotein	48.68 ± 9.744	53.84 ± 8.44	p=.0017
Triglycerides	120.36 ± 93.22	87.20 ± 39.94	p=.0880
Low Density Lipoprotein	141.08 ± 125.61	90.85 ± 21.13	p<.0001
Systolic Blood Pressure(mmHg)	118.78 ± 17.41	105.41 ± 6.54	p<.0001
Diastolic Blood Pressure(mmHg)	76.37 ± 10.97	67.46 ± 10.25	p<.0001
Waist Hip Ratio	0.87 ± 0.52	0.83 ± 0.03	p<.0001
BMI	24.02 ± 2.77	19.52 ± 2.90	p<.0001
HbA1c	10.35 ± 1.74	11.17 ± 2.46	p=.1101
ACE Medication (n, %) Yes No	 96.17% 3.83 %	 0% 100%	p>.10
Lipid Lowering Med (n, %) Yes No	 99.31% 0.69%	 0% 100 %	p>.10

Table 3.4 continued

Proliferative Retinopathy Yes No	 64% 36%	 0% 100%	 p<.0001
Overt Nephropathy Yes No	 68% 32%	 0% 100%	 p<.0001
Lower extremity Arterial disease Yes No	 92.33% 7.67%	 0% 100%	 p=.1473
Confirmed distal symmetrical polyneuropathy Yes No	 66.33% 33.66%	 97% 3 %	 p<.001
Coronary arterial Disease Yes No	 91.36% 8.64%	 93.76% 6.25%	 p=.2566

By Cycle 6, all 32 males had reached 18 years of age. Participants re-entered into the data set for longitudinal analysis at the cycle following their 18th birthday. Refer to Table 3.5.

Table 3.5 Cycles in which the 32 Males <18 at Baseline Re-Entered

Cycle	Frequency	Cumulative Frequency	Cumulative Percent
1	301	301	90.39
2	6	307	92.19
3	14	321	96.40
4	5	326	97.90
5	3	329	98.80
6	4	333	100.00

3.1.1 Protection of Human Subjects

The University of Pittsburgh Institutional Review Board (IRB) approval was obtained prior to participant enrollment and maintained as per University protocol for the time of study. Informed consents were obtained from the study participants. Each participant was assigned a unique identification number. Data collected for each participant was entered using the assigned number. To assure subject confidentiality, data forms were locked in the Epidemiology of Diabetes Complications Center.

Renewals and Modifications were completed as per University of Pittsburgh IRB protocols yearly. Author of this manuscript was a Co-Investigator. Refer to Appendix B: IRB .

3.1.2 Justification of Sample Size for Parent Study

Sample size determination for the projected EDC cohort of 800 was completed to assure that there would be a sufficient number of participants with specific risk factors and development of complications over the course of the study. Associations of various risk factors and complications were determined by selection of a sample of affected and a sample of unaffected matched on appropriate variables. Chi -square test statistics was used for dichotomous factors and t-test for continuous factors was used to detect statistically significant bivariate association. Sample sizes were calculated to detect sufficient power and effect.

Of the 333 males enrolled in the study at baseline, 298 were 18 years or older. Thirty-one (10.4%) males had prevalent ED. For this resultant prevalence, power was 0.67826, and beta was equal to 0.32174. Power desired for most epidemiological studies is ideally set to be .80 or .90 and under-powering a study could result in non-significant findings(Rothman et al., 2008). Since this power was below what is usually sought, precision was calculated to determine an estimate of the reliability to determine if the results would be generalizable. A sample size of 298 produces a 91% (±0.03072) confidence interval when the estimated proportion was 0.10. The wider the confidence interval, the less likely it will be to generalize the results (Rothman et al., 2008).

3.1.3 Measures

3.1.3.1 Dependent Variable

ED was used as the outcome measure, or dependent variable, and was defined as a persistent inability to attain and maintain an erection adequate to permit satisfactory sexual performance not due to any other problem as determined by the examining physician while conducting the Diabetes Control and Complications Trial (DCCT) clinical neurological examination protocol. ED was to be present for at least 30 days prior to the examination. Trained physician investigators inquired about autonomic neuropathy symptoms that included questions relating to 1) postural hypotension, 2) gastroparesis, 3) diabetic diarrhea, 4) colonic atony, 5) sudomotor abnormality, 6) hypoglycemic unawareness and 7) genitourinary autonomic neuropathy symptoms. ED was a "yes or no" determination after genitourinary system review by the examining physician. Prevalent cases were those males reporting ED at baseline exam (1986-1988), while incident cases were those males who were negative for ED at baseline but developed ED during a follow-up cycle (1989-2007). To determine incidence of ED, Cyles 1 through 6 and Cycle 10 were used. Cycles 7 and Cycles 8 were not used since these were sub-samples of the EDC participants. Inclusion of these two cycles could bias the results. The cycle in which the participant first reported ED following baseline examination was considered the incident cycle for ED.

In Cycle 1 thru Cycle 6, there were two measures of ED, one was physician determined after face-to-face interview and examination using the DCCT clinical neurological examination protocol and documented on the EDC-Medical Examination Form, while the second was self-

reported by the participant on the EDC-Medical History Questionnaire. This questionnaire was mailed to the participant 2 weeks prior to their EDC scheduled appointment. The participant or a participant designee could complete this mailed questionnaire. It was returned to the EDC at the time of the scheduled examination. The physician review response was used for the ED variable since it was thought to a more reliable indicator in determining if the erectile dysfunction was due to the diabetes process. However, in the event that the physician documentation was not available, consideration was given to whether the participant's self-report of ED could be used.

To determine if the self-reported ED variable could be used in place of the MD reported ED variable, a statistical test of agreement (kappa) was generated. This statistical determination had results indicating poor to good agreement dependent on the cycle and was not considered to be a reliable estimate of the ED variable in instances of missing MD reports. Refer to Table 3.6 for the cycle specific kappa coefficients. However, it was noted that despite non- statistical significance of the kappa statistic, the male participants reporting ED were 3 times [OR= 3.00,(0.6861-13.1184)] more likely to report ED if the physician examiner were male. This led to a further inquiry into whether this was the result of physician-gender bias. Sixty-two percent of the exams were completed by female physicians and 38% were completed by male physicians. There were 7 female and 6 male physicians who completed examinations throughout the 21 years of the EDC. All physicians were equally trained in completing the DCCT protocol examination. After a repeated measures analysis for within subject difference of self-report using participant self-reported response, the MD gender was not significant (p=0.4624); however, cycle 6 (p=.0023), cycle 3 (p=0.0392) and duration (p=.0191) were which suggests that the self-report was not affected by the gender of the examining physician.

but rather by participant response variability. Since the self-report variable was present for only the first six cycles, ED physician assessment was chosen as the ED measure.

Table 3.6:Kappa Statistic and 95% Confidence Interval for Physician Reported vs. Participant Self-Reported ED Cycles 1 thru Cycle 6

Cycle	Kappa Score	95% Confidence Interval
Cycle 1	0.4418	0.2515-0.6320
Cycle 2	0.6482	0.4361-0.8603
Cycle 3	0.4045	0.1427-0.6662
Cycle 4	0.5134	0.3066-0.7203
Cycle 5	0.6538	0.4681-0.8395
Cycle 6	0.5541	0.3968-0.7114

3.1.3.2 Independent Variables:

Demographic, psychosocial and behavioral variables were collected by self-report. Male participants completed the *EDC- General Medical History Questionnaire and EDC-Lifestyles Questionnaires.* (For a copy of this measure, please contact the PI of the Pittsburgh EDC). These questionnaires were mailed to the participant approximately two weeks before each scheduled appointment at the EDC Research Center. These questionnaires were completed by the participant and reviewed by the research staff prior to each biennial (cycle) visit. Cycles were approximately two years apart (refer to Table 3.2 for actual cycle dates). Variables of

interest were collected at baseline as well as Cycles 2 through 10 unless otherwise noted in the following descriptions.

Demographic Measures

Age was verified and recorded as age in complete years calculated from the participant's self-reported date of birth in month, day, and year at Cycle 1. Income, marital status and level of education were all self-reported by the participant on the EDC Lifestyles Questionnaire.

Income was adjusted accordingly over the course of the study. **Cycle 1-2** entered as 1= <$5,000/yr, 2=$5,000-$10,000/yr, 3=$10,000-$15,000/yr, 4=$15,000-$20,000/yr, 5=$20,000-$30,000/yr, 6=$30,000-$40,000/yr, 7=>$40,000/yr; **Cycle 3:** 1=<$10,000/yr, 2=$10,000-$20,000/yr, 3=$20,000-$30,000/yr, 4=$30,000-$40,000/yr, 5=>$40,000/yr, **Cycles 4-10:** 1=<$10,000/yr, 2=$10,000-$20,000, 3=$20,000-$30,000/yr, 4=$30,000-$40,000, 5=$40,000-$50,000, 6=$50,000-$60,000, 7=$60,000-$70,000, 8=>$70,000. These categories were then further collapsed based on the distribution of the income data to 1 of 3 income categories from; 1) $5,000/year to < $15,000, 2) $15,000 to <$30,000 and 3) >$30,000/year**.**

Marital Status was measured categorically as follows: 1) never married, 2) married, 3) separated, 4) divorced, 5) widowed, or, 6) not married, living with parent.

Highest Level of Education: Participant's answered as to their highest level of formal education and responses were coded as follows; 1=some high school, 2=high school graduate, 3=some college, 4= received bachelor's degree, and 5= graduate education beyond bachelor's degree. Due to the distribution of the data these then were recategorized into the following: 1) some high school/high school graduate, 2) some college, 3) college graduate/graduate degree.

Biologic Factors

Clinical samples and procedures were obtained and or performed by trained research physician/ personnel as per protocol. (See Appendix B Clinical Samples and Procedures)

***HbA1*:** Glycosylated Hemoglobin (HbA1) is a measure of diabetes control. The value reflects the level of circulating glycosylated hemoglobin for the past 120 days. A person without diabetes has a level below 7.3%. Levels above the normal (7.3%) are reflective of poor control and associated with the development of long term complications in those with existing diabetes. Laboratory values are continuous and were entered into the participant's data set and checked for accuracy. For the first 18 months of the EDC, HbA1 was determined by using saline-incubated blood and microcolumn cation exchange chromatography (Iso-Lab). Following the remainder of the 10 year follow-up, HbA1 was measured by an automated high performance liquid chromatography method (BioRad, Diamat). These two methods were found to be almost identical and highly correlated (r=.95). For Cycles beyond the 10^{th} year, HbA1c was measured using the DCA 2000 analyser (Bayer, Tarrytown, NY). The DCA and Diamat were also highly correlated (r=.95). HbA1 and HbA1c were converted to DCCT standard HbA1c values. The following conversion formula was applied to the first 10 years of HbA1 samples; DCCT HbA1=(0.83*EDC HbA1) + 0.14, while to the second 10 year EDC HbA1c samples the following conversion formula was applied; DCCT HbA1c=(EDC HbA1c-1.13)/0.81(Prince, Becker, Costacou, Miller, & Orchard, 2007).

***Duration of diabetes*,** a continuous variable, was calculated, at each biennial visit, from the month, day and year of diabetes diagnosis recorded at baseline. This was entered into the participant's data file in complete years.

Expiration/Inspiration (E/I) Ratio: This measure was collected in Cycles 2 through Cycle 10. A sub-study was completed in Cycle 1 measuring the E/I ratios of a sub-set of the

participant population. There were 92 males assessed (84 without ED and 8 with ED). Selected and trained research study staff completed the measurement procedure for the Expiration/Inspiration (E/I) ratio test. The E/I ratio, an autonomic nervous system function test, was measured with the participant in a supine position, limb EKG leads were attached and a lead II rhythm tracing recorded. The participant was then instructed to inhale deeply for 5 seconds followed by a forced expiration for 5 seconds and to continue this process of deep inspiration and forced expiration every 5 seconds for a total of 2 minutes. The participant was prompted by the examiner for determination of the 5 second intervals. The EKG was then marked to indicate an inspiration or expiration every 5 seconds during the recording for the total 2 minute testing time. After a one minute rest, the maneuver was repeated. Both the shortest R-R interval of each inspiration segment and the longest R-R interval of each expiration segment were measured in milliseconds. The E/I ratio was then calculated using the sum of six of the expiration (EXP) and inspiration (INP) R-R intervals using the following formula; sum of (R-R) EXP/ sum of (R-R) INP. Values < 1.1 were considered indicative of autonomic neuropathy (Stella, Ellis, Maser, & Orchard, 2000). Sensitivity of the E/I measurement is 0.93, specificity is 0.93, positive predictive value is 0.93 and negative predictive value is 0.94 (A Vinik et al., 2003). This variable was entered into the data set as a continuous variable.

Type and Number of Complications: There were 10 complications assessed for this analysis. Type and number of complications were measured as follows;1) *autonomic neuropathy (AN)* (confirmatory was an E/I ratio < 1.1 while an E/I ratio > 1.1 was considered negative for AN), 2) *Confirmed Symptomatic Autonomic Neuropathy (SAN)* was defined as having an average E/I Ratio of <1.1 and 2 or more of the other autonomic symptoms as

determined by the examining physician using the DCCT neuropathy protocol previously described**,** 3) *Distal Symmetrical Polyneuropathy (DSP)* was measured using the DCCT protocol and defined as clinically evident diabetic peripheral neuropathy confirmed by physician's exam (defined as at least 2 of the following symptoms consistent with DSP; confirmatory symptoms included either an abnormal sensory exam consistent with DSP, or decreased or absent deep tendon reflexes), 4) *Confirmed distal symmetrical polyneuropathy (CDSP*) was clinically evident diabetic peripheral neuropathy consistent with DSP confirmed by physician's exam and vibratory threshold of >2.39 for ages <36 years, > 2.56 for ages 36-50 years, and >2.89 for ages > 50 years. EDC protocol for measurement of the vibratory threshold procedure included the following: The participant was instructed to use the index finger of his or her dominant hand and press against each rod in sequence for approximately one second. During each trial the participant was allowed to touch the rods only once. Only one of the rods would be vibrating and the participant had to decide whether it was the right or left rod. The task became increasingly more difficult with each of the trials. For this procedure, threshold determination was as follows; a number of vibration intensities were set and sampled by the participant. This was done to determine the appropriate voltage level at which to begin testing. After each correct choice, the intensity was decreased by 10 %. When the participant made an error, the same intensity was repeated for two additional trials. If two of the three trials were correct, the intensity was decreased. If two of the three trials were incorrect, the intensity was increased. Testing was continued until a total of five errors were made. The procedure was repeated using the participant's great toe of his/her dominant side. The threshold was determined by recording the vibratory values of the five errors and the five lowest correct scores. The highest and lowest of these ten scores were eliminated. The mean

of the remaining eight scores was used to determine the absolute vibratory threshold. Data were coded as none (0), DSP (as defined above) and vibtoe negative (1), DSP and vibtoe not available (2), and, DSP and confirmed with vibtoe (3), 5) Resting ankle and arm blood pressure readings, using a Doppler Flow Detector, and the participant in the supine position, were used to determine the presence of *lower extremity arterial disease (LEAD).* Ankle-brachial pressures were calculated using the arm pressure taken closest in time to the ankle pressure. Any participant with an ankle-brachial index (AB) of <0.8 for any of the four vessels or a history of claudication or of amputation for vascular reasons was considered positive for LEAD. Data were coded as none (0), or AB<.8, amputation or claudication (1), 6) *Overt nephropathy (ON)* was measured as an albumin excretion rate >200micrograms/min in multiple timed urine specimens, renal dialysis or a kidney transplant. Data for ON were coded none (0), or overt or renal failure (1), *7) Coronary artery disease (CAD)* was measured as a history of MI (confirmed by ECG Q-waves or hospital records, using standardized criteria), coronary arterial occlusion (>=50 % by angiography, myocardial infarction (Minnesota codes 1.1, 1.2), ischemic ECG (Minnesota codes 1.3, 4.1-4.3, 5.1-5.3 or 7.1) or revascularization at the 10 year-examination, or diagnosis of angina by the EDC study physician during any cycle (Prince et al., 2007), *8) Cerebral Vascular Disease (CBVD)* was ascertained by history by the examining physician and measured as none (0), or definite stroke (2), *9) Proliferative retinopathy* was determined from fundus photography and measured as none (0), retinopathy and/or laser treatment of retinopathy (1), and *10) Hypertension* was defined as a blood pressure greater than 140/90 mmHg or on anti-hypertensive medication.

Total number of complications: Using the following: CAD, CDSP, LEAD, overt nephropathy and proliferative retinopathy, a summation score was calculated. Score range was

from 0-5 with the higher number indicating more complications. Hypertension was assessed separately. AN and SAN were not included in the total number of complications because measurement at baseline was available for only 27% of the male participants (84 without ED and 8 with ED).

Systolic and Diastolic blood pressure: Trained EDC research staff measured blood pressure per Hypertension Detection and Follow-up Protocol using a random zero sphygmomanometer. Mean of the second and third blood pressure readings were used and entered as a continuous variable for systolic and diastolic pressures separately.

Lipid Profile: *High density lipoprotein (HDL)* was determined by means of precipitation (heparin-manganese chloride method)(Warnick & Albers, 1978). This lipid sub-particle is believed to be protective for cardiovascular disease. Triglycerides (Bucolo & David, 1973) as well as plasma cholesterol were measured enzymatically (Allain, Poon, Chan , Richmond, & Fu, 1974). Low density lipoprotein (LDL) is the cholesterol sub-fraction associated with the development of plaque within the arteries that contributes to the development of atherosclerosis. Levels below 100mg/dL are clinically associated with lower risk for development of cardiovascular disease. LDL was measured by using the Friedwald equation (LDL Cholesterol=Total Cholesterol.- High Density Lipoprotein cholesterol - Triglycerides/5) (Friedewald, Levy, & Fredrickson, 1972). For this analysis, *non-High Density Lipoprotein (HDL) cholesterol* was calculated as total cholesterol minus HDL.

Lifestyle Behavior

Smoking status: Smoking status was coded as "ever smoked 100 cigarettes" 0=no, 1=yes. Ever smokers were then directed to answer "current smoker" 0=no, 1=yes.

Alcohol Intake: In addition to the average number of alcoholic beverages consumed per week, data were also collected for type of alcohol consumed, i.e., beer (12 oz), wine (4 oz), or liquor (shots). Average number of alcoholic beverages was entered into the database as well as type of alcohol consumed. In addition to the continuous alcohol variable (to reflect mean of alcohol consumed per week), a categorical variable was created; 0=no alcohol, 1=1 to 3 drinks per day, 2=>3 drinks/day. This variable was created to show the difference in group membership by ED status.

Anti-hypertensive medication:

Participants were asked to self-report medication used for hypertension. To qualify as a blood pressure medication (ant-hypertensive medication) the medication had to be used to treat hypertension in the participant.

Psychosocial Measures

Quality of Life: This was measured by a modified version of the Diabetes Control and Complications Trial (DCCT)-Quality Of Life (QOL) instrument, and, referred to as modified DCCT-QOL (mDCCT-QOL: By self-report, on the EDC Lifestyle Questionnaire, quality of life was assessed by a modified version of Diabetes Control and Complications Trial Quality Of Life (DCCT-QOL) instrument. The DCCT-QOL was developed for use in the Diabetes Control and Complications Trial (DCCT) to compare the relative personal burden for participation in either the intense treatment group or standard care group for insulin therapy. There were 46 questions divided into four domains that included the following; impact (20 questions), worry-social/vocational (7 questions), worry-diabetes related (4 questions) and satisfaction (15 questions) (Group, 1988). Cronbach's alpha for this measuresment used in the DCCT was 0.92.(DCCT, 1988). The modified DCCT-QOL *(mDCCT-QOL)* measure

contained 14 of the original 20 item questions in the impact domain, all of the 7 questions from the worry-social/vocational domain, and 3 of the original questions from the worry-diabetes related domain. Responses to questions within each of these domains were made on a 5-point Likert scale. Impact and worry scales were from 1 (no impact and never worried) to 5 (always impacted and always worried). Impact total scores ranged from 14-70. Worry total score ranged from 11-66. The higher scores indicating more impact and worry. Satisfaction was surveyed using 3 general questions: one question responses were "very satisfied, fairly satisfied, or, not very satisfied". Scores for this question ranged from "very satisfied"(1) to "not very satisfied"(3). The other 2 questions, questions of comparison for general health compared to other persons their age with and without diabetes, were scored using a Likert scale from 1 (excellent health) to 4 (poor health). Total score range for satisfaction was from 3-11, the higher score indicating less satisfaction. Total mDCCT-QOL scores ranged from 28-147, higher scores indicating more impact and worry from diabetes and less satisfaction with the quality of life. In addition to the total mDCCT-QOL score and the domain scores there was one question within the impact domain that was reviewed separately for this study. This question (#9impact domain), "How often does your diabetes interfere with your sex life" was answered on a Likert scale from 1-5, 1 being "never" to 5 being "all the time". Scores for this question ranged from 1-5, higher score indicating more interference. Cronbach's alpha for the total mDCCT-QOL for this EDC population was 0.8348. Cronbach's alpha scores for each of the three domains were as follows; impact (Cronbach's alpha=0.784), worry (Cronbach's alpha =0.714), and satisfaction (Cronbach's alpha=0.710).

Depression: The Beck Depression Inventory (BDI-II) is an instrument used to measure self-reported depressive symptoms. This measure was part of the *Epidemiology of Diabetes*

Complications Lifestyle Questionnaire. (For a copy of this questionnaire, please contact the PI). It was included in the packet of questionnaires that was sent to the participants two weeks prior to their scheduled research clinic appointments and was collected at baseline as well as each biennial visit. The BDI was developed by Dr. Aaron Beck in the early 1960's. The BDI contains 21 items and two dimensions. The first domain is the Somatic-Affective domain measuring somatic symptoms such as fatigue and loss of energy. The second domain, the Cognitive domain, is associated with such psychological symptoms as pessimism and worthiness. There are 4 ordered responses in intensity and are coded from "0" to "3" Scores can range from 0 to 63, and are calculated by summing the number that corresponds to the symptom level self-reported by the participant (Beck, 1961). Participants were instructed to answer the questions based on the way they were feeling during the past week. High scores (ranging from 29 to 63) indicate severe depressive symptoms. Scores ranging from 20 to 28 indicate moderate depressive symptoms, whereas, scores ranging from 14 to 19 indicate mild depressive symptoms. Those with total scores between 0 and 13 were considered not to have any depressive symptomatology. Cronbach's alpha for internal consistency for the total score is 0.88. The BDI –II was positively correlated with the revised Hamilton Psychiatric Rating Scale for Depression (r=.71) for construct validity (Beck, 1961). There were 2 previous versions of the BDI which have been revised for clinical use. The latest version was derived to reflect the diagnostic criteria for major depressive disorders that are described in the American Psychiatric Association's Manual of Mental Disorders, Fourth Edition (DSM-IV). At baseline there were 39 missing BDI scores. Since these missing represented 13.1% of the male participants, an analysis of the missing was completed to assure that these were indeed missing by random. Thirty-five of these males were ED negative, while 4 were ED positive.

Characteristics of the participants with missing BDI scores were not significantly different in age (p=.051), systolic blood pressure (p=.3690), diastolic blood pressure (p=.136), duration of diabetes (p=.725), or DCCT corrected Hba1 (p=.682) than those participants with BDI scores.

Behavioral and Cognitive Measures

Self- Management Behavior: For this study, there were 3 questions that were to be combined to form the self management behavior variable of interest for this secondary data analysis. Unfortunately, the self-efficacy, knowledge and perception of severity variables were only measured at baseline. Therefore, the analysis was only completed to compare those with prevalent ED to those without ED. These questions were part of the more inclusive Diabetes Measure for Attitudes, Behavior and Self Care which was also included for participants' response and contained within the Epidemiology of Diabetes Complications General Medical History Questionnaire. The Diabetes Measure for Attitudes, Behavior, and Self Care (Rand) was a brief, valid and reliable self-report of diabetes management that contained assessment of diet, exercise, blood glucose monitoring, and beliefs and attitudes toward diabetes. There were 3 questions of interest used to define self-management behavior and were as follows, response choices were yes or no; 1) Have you tested your urine or blood for glucose or sugar at least once a week during the last 12 months? 2) If your urine sugar is running high, do you make any changes in the following? Diet: yes, no, Exercise: yes, no, Insulin usage: yes, no, 3) If your blood sugar levels are running high, do you make any changes in the following? Diet: yes, no, Exercise: yes, no, Insulin usage: yes, no. Questions #2 and #3 were combined and recoded as 0=no and 1=yes if the participant changed diet, exercise or insulin usage according to either blood or urine tests.

Self Efficacy: For this measure, the following question was chosen from the EDC-Lifestyles Questionnaire as an indicator of self-efficacy and coded as follows; "Do you believe that you can do something to prevent or delay the occurrence of these long term complications?" 0=no, 1=yes, 2=don't know.

Perception of Severity: This variable was assessed by the following 2 questions; 1) Do you believe the controlling of your blood sugar would prevent or delay the development of these long term complications? 0=no, 1= yes, 2=don't know and, 2) Do you believe that controlling your blood sugar would make the complications less severe if they developed? 0=no, 1=yes, 2=don't know. Each question was assessed separately.

Knowledge: This variable was assessed by the following question: How would you rate your overall knowledge of diabetes? 0=poor to fair, 1= good to excellent.

For the above variables of self management, knowledge, perceptions of severity, and self efficacy, content validity was established through behavioral experts.

3.2 ANALYSIS PLAN

3.2.1 Data Accuracy and Appraisal of Missing Data

The EDC had an established data quality control procedure. Data forms were reviewed and coded by the data manager in the EDC. Questions about the validity of values were forwarded to the study coordinator and/or the principle investigator. One individual performed the data entry then all forms were subsequently double keyed by an additional staff member or student researcher. Should discrepancies between the two entries exist, the two entries were reviewed

and resolved by the data manager. Data cleaning consisted of checking the accuracy and validity of the data, including checking the range of values for each item and comparing responses among related items. Data cleaning occurred on an ongoing basis, to give timely feedback. When appropriate, missing values were substituted with answers provided on other surveys or imputed from prior data. Values that remained missing were assigned classification codes for missing values.

For this analysis: The accuracy of the data was checked by comparing the range of the values, minimum and maximum values, missing data, and patterns of missing data. Of the baseline data, adjusting for age greater than 18 years, missing baseline data for ED status and one multivariate outlier (n=297), there were 8 variables identified with missing values. They were BDI total score (n missing=39, 13%), income (n missing=57, 19%), hypertension status (n missing=1), retinopathy status (n missing=3), ACE medication (n missing=13), lipid medication (n missing=12), and smoking ever status (n missing=9). The values with greater than 5% missing were evaluated further. BDI score was previously presented in this chapter and determined that those with missing BDI scores g were not statistically different from those participants with recorded BDI scores. The variable income was evaluated. This variable differed from the non-missing in age, BDI score, and duration of diabetes. This variable did not differ by education, complication status, ACE medication, lipid medication or diabetes control. When describing the sample, this was noted.

3.2.2 Exploratory Data Analysis:

Two statistical software programs were used; SPSS (Statistaical Software Package for the Social Sciences, Versions 15 and 16, 2007 and 2008) and SAS (version 9.1 and 9.2, Cary, NC

2007 and 2008). SPSS was used to generate preliminary statistics to characterize the sample, explore missing values of the variables, detect outliers and evaluate the underlying assumptions of linearity, normality and homoscedasticity. The planned analysis (logistic regression) uses a binomial distribution, and therefore the assumption of normality was relaxed. However, there was still a necessity to determine normality of the variables to choose the appropriate parametric or non-parametric comparison test. Using the exploratory data generated, there were appropriate numeric summaries, visual displays and graphs that further investigated these relationships between the independent and dependent variables of interest. For the descriptive statistics, SAS was used to generate means and standard deviations calculated as measures of location and spread for all continuous variables, while contingency tables were generated to test the categorical variables. Continuous variables were assessed for skewness and kurtosis and through graphical representation using a histogram. Correlations were determined through Pearson's correlation coefficient and Spearman's rank correlation coefficient where appropriate. Data were checked for multicollinearity within the covariance matrix. Correlations, variance inflation factors (VIF), tolerance and condition indices were used to identify inter-correlations and redundancies among the variables. All correlations with the exception of age and duration, confirmed distal symmetrical polyneuropathy (CDSP) and distal symmetrical polyneuropathy (DSP) were below 0.8, VIFs' <10, tolerance values >0.10 and condition indices <30. Age and duration of diabetes were highly correlated ($r=.89$, $p<.0001$). Adjusting for both age and duration when modeling could not occur simultaneously. Duration was therefore chosen. However, separate analyses were conducted using age in place of duration and similar results were obtained. CDSP and DSP ($r=.94$, $p<.0001$) were also highly correlated. CDSP was chosen as the variable for the analysis.

3.2.2.1 Outlier assessment (univariate/multivariate)

An outlier is a case of an extreme value on one variable, termed a univariate outlier, while multivariate outliers have unusual combinations of scores of two or more variables (Tabachnick & Fidell, 2001). Outliers may impact the regression coefficients. Categorical variables were investigated by determining the splits over categories while the continuous variables employed descriptive statistics for determination of range, minimum and maximum. Also for the continuous variables, stem and leaf plots, histograms, box plots, and normal probability plots were used to assess extreme values. Z-scores were computed to assess how extreme the identified univariate outliers were. If a z-score was greater than the critical value of 3.29, or less than the critical value of 3.29, the data point was considered an outlier (Rosner, 2000; Tabachnick & Fidell, 2001). Assessment of multivariate outliers was completed by computing Mahalonobis distance. Mahalonobis distance, the distance of the case from the centroid of the remaining cases where the centroid is the point created at the intersection of the means of all the variables (Rosner, 2000; Tabachnick BG, 2001), has a chi-square distribution with degrees of freedom based on the number of variables being assessed. Conservative estimate cut points are $p<0.001$ for the chi square value. There were several univariate outliers that impacted the distribution, with z-scores greater than/less than 3.29. These were then further evaluated by deleting them from the analysis, i.e. sensitivity analysis. However, after deletion, since no change resulted, these values were allowed to remain in the analysis. There was one multivariate outlier identified. This multivariate outlier was also identified as a univariate outlier as well, with extreme values for duration of diabetes, systolic blood pressure and HbA1. Since this participant was identified as an incident ED case, a decision was made to retain the observation. Separate analyses were then conducted, with this multivariate outlier

in the dataset and a second time with this multivariate outlier deleted from the dataset. Since there was a significant difference after conducting this exploratory analysis (Rosner, 2000; Tabachnick BG, 2001), the decision was made to delete this data point. .

3.2.3 Data Analysis Procedures

The following were the data analysis procedures used according to each specific aim.

Specific Aim #1: Determine both the age specific prevalence and incidence of ED as measured by self-report during physician interview

Question #1a: What was age-specific prevalence of ED for males enrolled at baseline as compared to age specific normative data?

Prevalence was defined as the number of cases per population at risk(Jewell NP, 2004). It was important to calculate the prevalence of a given disease because not only does this rate measure the amount of illness within a certain population at a specific period of time but the rate can theoretically help determine the health care needs of the population at risk(Jewell NP, 2004). Age-specific rates were calculated for particular age groups at baseline. The numerator and the denominator refer to the same age group, or in other words both have the same age distribution. These age specific rates were calculated to display certain aspects of the ED health experience, i.e., by generating these rates it was possible to determine if ED occurred more frequently in the younger age groups. Since there were no normative data for comparative purposes, this could not be determined. Had this step in the analysis been able to be completed, it would have shown if the ED experience in this EDC population was different from that of the general population. In the ED literature, the age specific categories were

usually in 10 year increments. Age categories for this analysis were within the 18 to 47 year range.

Overall prevalence rate per 1000 was calculated for ED using the following formula: (*Number of cases of ED present at baseline / Number of eligible males at baseline) x 1,000.*

Age specific prevalence rates were computed for the ED cases present at baseline. Age categories were chosen because of the age range of the enrolled males in the EDC study: Ninety-five percent confidence intervals were generated for these rates to determine if the number of cases were significant for that particular age group. The age groups were as follows: 18-29 years, 30-39 years, and 40-49 years.

As previously stated, there were no normative data found to compare this sample. The age specific rates reported in the literature that were appropriate, either due to definition of ED used or research methodology, were age specific rates for age groups starting at ages 40 years and older. There was no NHANES data to compare as ED only became a variable of interest for this national survey starting in 2000.

Question #1b: What was the age-specific incidence of ED?

The incidence rate directly estimates the probability of developing a disease within a specific period of time and is defined as the number of "new cases" per population at risk. These rates are used not only to determine the probability of developing a specific disease but also to determine /detect etiological factors.

Calculation for Incidence rate per 1,000 was as follows:

(Number of new cases of a disease occurring in a population during a specified period of time / Number of persons exposed to risk of developing the disease during that period of time) x 1,000.

The age-specific rates were computed by limiting the population at risk to a certain age category. Ninety-five percent confidence intervals were calculated for these rates to determine if the number of cases were significant for that particular age group.

The Kaplan-Meier survival analysis method was used to generate a table and plot of survival or hazard functions for ED history data (time to ED data) . This model was not used to assess the effects of the covariates on ED event. It was used to provide descriptives for the time-to-ED event using the cycle time as the salient variable. Since there were censored observations (e.g., participants who were lost to follow-up) within the EDC dataset, the Kaplan Meier estimation estimated survival functions when censoring occurred. . The Kaplan-Meier curve is estimated by calculating the number of participants who do not have an ED event divided by the number of participants at risk. Participants who have not reached that time point or who were censored were not counted in the at risk group. The probability of surviving (not having ED) to any time point was then estimated from the cumulative probability of surviving (not developing ED) at each of the preceding cycle time points. It should be noted that the precision of the Kaplan –Meier estimate was dependent on the number of total observations.

Specific Aim #2: Determine baseline predictive risk factors for the development of ED

Question #2a:Which baseline demographic factors (age, income, marital status, level of education, smoking, alcohol intake), biologic factors [HbA1c, age at diagnosis, duration of diabetes, E/I ratios, type and number of complications, systolic and diastolic blood pressure, lipid profile (HDL and nonHDL cholesterol] lifestyle behaviors (smoking, alcohol intake), and, anti-hypertensive medication use predict prevalent and incident cases of ED?

Question #2b: Do baseline psychosocial factors [quality of life (modified DCCT-QOL Questionnaire)], and depression (Beck Depression Inventory)] predict ED?

For both research questions, binary logistic regression analysis was used to investigate the relationship between the binary dependent variable, ED, and the independent explanatory variables or covariates. As with, and in common with, standard linear regression, logistic regressions' primary objective is to relate the probability of a response to a set of covariates (Rosner, 2000). Since the outcome of interest, ED, was binary and the predictors tested for associations were both discrete and continuous it was necessary to use a modified regression technique to assess the probability of the male experiencing the ED outcome. The outcome was expressed as a proportion, and the predictor variables were expressed as log-odd ratios. A link was necessary to make the outcome linear. Link is defined as a non-linear transformation applied to μ to enable the transformed probabilities to be related linearly to $X_{i,..}$ All continuous variables were evaluated to assure that they were linear in the logit. This was completed by multiplying the natural log of the variable by the variable and then regressing this product on the outcome variable. The variable was considered linear in the logit if the regression co-efficient had a p-value >.05. Statistically this was explained as the raw outcome, which is expressed as a proportion, was converted to a linear function with the logit link function of the form of:

$$\text{Logit}(x) = \ln [p(x)/1+p(x)] = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_k x_k$$

Whereby, x is the vector of k predictor variables from the i-th participant. The set of predictor variables for this analysis included; baseline demographic factors (age, income, marital status, level of education), biologic factors [HbA1c, age at diagnosis, duration of diabetes, E/I ratios, type and number of complications, systolic and diastolic blood pressure, lipid profile (HDL,

nonHDL)], lifestyle behaviors (smoking and alcohol use) and antihypertensive medication use as well as the psychosocial variables (QOL, depression) given the predictors equals p(x) is the following:

$$p(x)=exp^{(\beta_0+\beta_1x_1+\beta_2x_2+\ldots\beta_kx_k)} / 1+ exp^{(\beta_0+\beta_1x_1+\beta_2x_2\ldots+\beta_kx_k)}$$

Calculation of the odds ratio for the outcome associated with the individual predictor variables was calculated by exponentiation of the regression co-efficients. Maximum likelihood estimation (MLE) was used to find the regression coefficients. This was an iterative process that starts with arbitrary values of the co-efficients and determines direction and size of change in the coefficients that maximize the likelihood of obtaining the observed frequencies(Tabachnick & Fidell, 2001). It was necessary to use MLE in order to estimate the parameters associated with the predictor variables to make inferences about the parameters in the model. The most parsimonious model was constructed to determine the predictor variables. A selection model with variable entry set at 0.15 and determination of the predictor variables set at 0.05 was used to determine the best fitting model. Predictor variables were assessed for model fit by using the Wald Chi square statistic set at p-value less than or equal to 0.05. Model improvement was determined by using the -2log likelihood (p-value less than or equal to 0.05). Goodness of fit of the model was assessed using the Hosmer-Lemeshow Test with a p-value greater than 0.05. SAS (PROC LOGISTIC) was used as the statistical software for the logistic regression procedures with exact options since some of the predictor variables had SPARSE cells <5 (Hosmer & Lemeshow, 2000). All models for SA #2a were adjusted for duration of diabetes whereas the models for SA#2b were adjusted for duration of diabetes and total complications.

Cox proportional hazards modeling, a method that describes how the hazard or risk changes over time, was used to show the prospective relationship of predictive variables to incident ED outcome. All variables that were significant univariately, p-value set at less than or equal to 0.15, were then evaluated for their independent relationship to ED development in the multivariate model.

Specific Aim #3: Determine the sequence of the development of ED to other markers of neuropathy, i.e., Cardiac Autonomic Neuropathy (CAN defined as an E/I ratio <1.1), Confirmed Distal Symmetrical Polyneuropathy (CDSP), and Symptomatic Autonomic Neuropathy (SAN) (excluding ED) using longitudinal data.

Question# 3a**:** What was the sequence to the development of ED in relation to other markers of neuropathy, i.e., CAN, CDSP, and SAN?

Cox proportional hazards model was constructed for the longitudinal data with time dependent covariates. The primary goal of this analysis was to determine if predictor variables the cycle preceding the ED event were independent predictors for incident ED.

Secondary Specific Aim: Determine behavioral and cognitive risk factors, as represented by self-management behavior, self-efficacy, perception of severity and knowledge associated with the development of ED using EDC longitudinal data.

Question #1.: Did self-management behavior, self-efficacy, perceptions of severity and knowledge of diabetes predict ED?

For this analysis, the longitudinal predictor covariates of self management, self-efficacy, knowledge and perceptions of severity in their relationship to the outcome variable of ED and their time dependent manner were to be used; however the variables, knowledge,

perception of severity and self-efficacy were only collected at baseline. The longitudinal assessement of these variables therefore could not be completed.

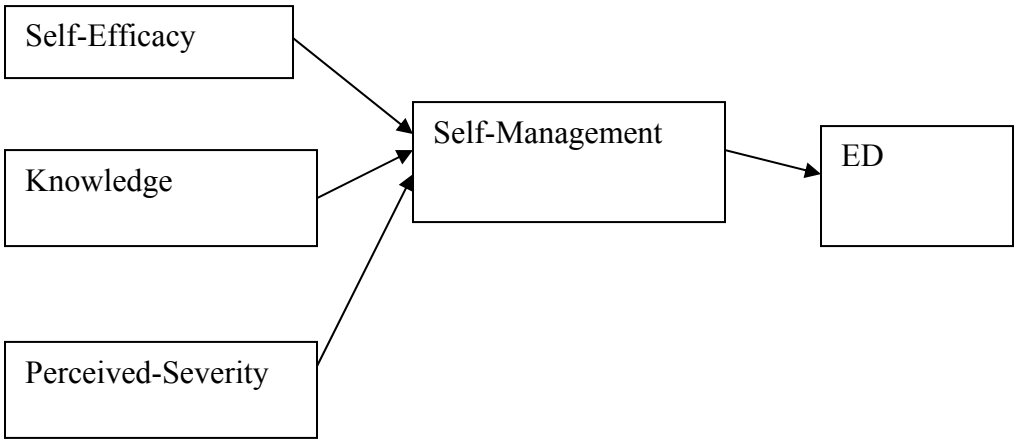
Question #2: Is self-management a mediator between cognitive variables (self-efficacy, perceptions of severity and knowledge) and ED?

Path Analysis, an extension of multiple regression, was to be used for this longitudinal analysis. However, the data was not available beyond baseline.

Explanation of Path Analysis: This analysis form would have been used to test the fit of the correlation matrix against two or more casual models which are used in the comparison. A regression would have been done for each variable in the model as dependent on others which the model indicates as causal. The regression weights predicted by the model are compared with the observed correlation matrix for the variables and a goodness-of-fit statistic is calculated. Path coefficients were used to assess the relative importance of various direct and indirect causal paths to the dependent variable. There are several assumptions that need to be met for path analysis: 1) relationships among variables must be linear , 2) there are no interaction effects, 3) Interval level data are needed for all variables, if regression is used to estimate the path parameters, 4) Residual variables, or unmeasured variables, are uncorrelated with any of the variables in the model other than the one they cause, 5) Disturbance terms are uncorrelated with the endogenous variables, 6) Low multicollinearity, 7) appropriate correlational input, i.e., Pearson correlation for two variable intervals, polychoric correlation for two ordinal variables, tetracholoric for two dichotomies and polyserial for an interval and an ordinal variable. To test for mediation, it is necessary to test the following three regression equations. First, it is necessary to regress the mediator on the independent variable. Second, the dependent variable is regressed on the independent variable, and third, regression of the

dependent variable on both the independent variable and on the mediator. Path diagrams are used to show the models considered. In this study, ED is the dependent variable, and self management behavior is the mediator variable. Self-efficacy is the independent variable, as are knowledge and perceptions of severity. The hypothesized path is a follows in Figure 3.1:

Figure 3.1: Mediation Model Path Diagram of Self-Management Behavior and ED Outcome



Mediation variables account for the relation between the predictor and the criterion. The above Figure depicts the causal pathways to the outcome of ED, 1) the direct impact of the independent variable or path c, the impact of the mediator, path b and finally the impact of the independent variable to the mediator, path a. *A variable functions as mediator after meeting the following three conditions; 1) variation in levels of the independent variable significantly account for the variations in the presumed mediator (path c), 2) variations in the mediator significantly account for variations in the dependent variable (path b) and 3) when paths a and*

b are controlled, a previously significant relation between the independent and dependent variables is no longer significant with the strongest demonstration of mediation occurring when path c is zero (Baron, 1986).

Exploratory path analysis could not be completed to examine the relationship between knowledge, perceptions of severity, self-efficacy, self management behaviors and ED. Criterion for examining the goodness of fit of the model would have included a chi square probability greater than or equal to 0.05, with a Comparative Fit Index (CFI) or at least 0.90. (Norris, 2005: Steele, 2005). SPSS would have been used to run the analysis.

Correlation statistics were generated for these behavioral and cognitive risk factors. Descriptive statistics were also generated for the baseline variables (self-management behavior, self-efficacy, perception of severity, and knowledge associated with prevalent ED.

4.0 MANUSCRIPT ONE

4.1 ABSTRACT

Objective: The purpose of this study was to examine the overall prevalence and incidence of ED self-reported in males with T1D during physician exams enrolled in the Pittsburgh Epidemiology of Diabetes Complication (EDC) study from 1986 to 2007 and determine significant baseline demographic, biologic, behavior lifestyle, anti-hypertensive medication usage, and, psychosocial risk factors for the prevalent and incident cases of ED.

Methods: In a large population-based cohort study of type 1 diabetes, 333 males enrolled at baseline were followed biennally for a period of 21 years for ED development. Two separate multivariate models, using logistic regression for the prevalence (Model 1) and Cox proportional hazard regression (Model 2) for the incidence, were constructed. After controlling for duration of diabetes, Model 1 identified associated demographic, biologic, lifestyle behavior, use of anti-hypertensive medication use as risk factors, while Model 2 identified only psychosocial risk factors.

Results: Mean age of the males at baseline with ED was 35.8 ± 5.3 years and mean duration of diabetes was 26.9±5.9years. *Prevalence rate* was 10.4 %, with 31 males having ED at baseline. Males at baseline, with ED, had higher systolic and diastolic blood pressures, and had 3.21 (95% C.I. 1.4-6.6, p=0.0021) and 3.8 (95% CI 1.45-9.96, p=0.0106) times the odds to

have hypertension and CAD, respectively, than those males without ED. Males with prevalent ED did not statistically differ from males without ED in the baseline characteristics of metabolic control (HBA1), level of education, income, or the current use of ACE or lipid lowering medication. However, males with prevalent ED had 6.27 (95% CI 2.12-10.18, p=.0210) times and 4.65 (95% CI 2.12-10.18, p=.0053) times the odds to have proliferative retinopathy and overt nephropathy respectively than those males without ED. For the baseline logistic regression model, multivariate risk factors identified for Model 1 were CDSP and HDL. There were no demographic or lifestyle behavior risk factors that remained in the model. Use of anti-hypertensive medication was not a significant predictor. The significant logistic regression independent predictor for Model 2 was the BDI depressive symptomatology score. Fifty-four new cases of ED were reported. *Incidence* was 17.78 % , with person time at risk equal to 2034 person years during the 18 years of follow-up. Thus, the incident rate was 2.60/ 100/year. Mean age for the incident cases was 40.6 ± 5.9 (range 26.7-60.8) years while the mean duration of diabetes was 32.54 ± 5.88 (range 20.9-51-9) years at diagnosis. Mean systolic and diastolic blood pressures were 125. 2 ± 20.5 (range 88.0-191.0) mmHg and 75.57 ± 11.36 (range 49.0-108.0) mmHg respectively. Mean HbA1 was 10.68 ± 2.19% for cases. The mean E/I ratio for these incident males was 1.14 ± 0.122 (range 1.0-1.55) and mean BDI depressive symptomatology total score was 9.5 ± 6.9 (range 0-32). Ninety percent of the incidence cases were between 30 and 49 years of age. Multivariate predictors for Model 1 (Cox Proportional Hazard Regression) included CDSP, nonHDL cholesterol while significant Model 2 (Cox proportional Hazard Regresssion) predictor was total BDI depressive symptomatology score.

4.2 INTRODUCTION

An estimated 12.0 million (11.2%) men aged 20 years or older in the United States have diabetes (NIH, 2007). Among the most prevalent long-term complications that may result from diabetes is erectile dysfunction (ED). Males with type 1 diabetes (T1D) are twice as likely to develop ED than males without diabetes (Bacon et al., 2002; Bacon et al., 2003; http://www.diabetes.org/diabetes-statistics/complications.jsp, 2007; A Vinik et al., 2003).

The etiology of ED in men with T1D is multifactoral. Once thought to be purely psychogenic in origin, it is now recognized that approximately 80% of all ED results from vascular, neuropathic , and /or endocrinological etiologies in males with diabetes (Blumentals et al., 2003; Dean & Lue, 2005; Garban et al., 1995; Saenz de Tejada et al., 2005). Biological risk factors of increasing age, longer duration of diabetes, poor metabolic control, associated chronic complications of diabetes including hypertension, dyslipidemia, cardiovascular disease, neuropathic disease, and depression have been confirmed by numerous studies (Burnett, 2006; Fedele, 1998; Klein et al., 2005). Also previously reported associated risk factors for ED development include; demographic factors of age, income, marital status, and level of education, psychosocial factors affecting quality of life (Burnett, 2006; DeBeradis et al., 2002) and lifestyle behavioral risk factors include smoking and alcohol ingestion ,(Burnett, 2006; Close & Ryder, 1995; Enzlin, 2003; Fedele, 1998; Klein et al., 2005).

Many of the same risk factors are shared by ED and cardiac disease development and progression in males with T1D. Like ED, males with diabetes have a 2-fold increase in developing cardiac disease. ED may be considered an important marker in the development and progression of cardiac and vascular disease (Kloner, 2008b). Although it is known that males with diabetes have a higher incidence of coronary artery disease (CAD) than those

without diabetes, the risk is even greater for males with diabetes who have ED. In a recently published study (Gazzaruso et al., 2008), males with type 2 diabetes were more likely to report ED four years before the development of a major adverse cardiac event (Gazzaruso et al., 2008; Kloner, 2008b) Moreover, males with ED and T1D have an increase in the severity of coronary heart disease, as well as neuropathic disease (A Vinik & Erbas, 2001). Thus an association between the onset of ED, CAD and neuropathy is well established.

Those with ED and diabetes experience an earlier mortality than males in the general population without diabetes which may be isolated or coexist with other diabetic complications or peripheral neuropathies (A Vinik & Erbas, 2001). Since it is estimated that in the year 2025, there will be more than 322 million men worldwide with ED, it is necessary to develop preventive strategies in males likely to develop ED (DeBerardis et al., 2007).

Therefore, the purpose of this study was to examine ED self-reported in males during physician exams enrolled in the Pittsburgh Epidemiology of Diabetes Complication (EDC) study (1986-2007), a large population-based cohort study of type 1 diabetes. The specific aims of this study were to: 1) determine both the age-specific prevalence and incidence of ED in the EDC population; and 2) determine significant baseline demographic, biologic, lifestyle behavior risk factors, anti-hypertensive medication and psychosocial risk factors associated with prevalent and incident ED. Baseline demographic factors include: age, income, marital status, and level of education. The baseline biologic factors include: HbA1c, age at diagnosis, duration of diabetes, E/I ratios, type and number of complications, systolic and diastolic blood pressure, lipid profile [High Density Lipoprotein (HDL) and non-HDL cholesterol]. Baseline lifestyle behavior risk factors include: smoking and alcohol intake. Baseline Anti-hypertensive

medication use and baseline psychosocial risk factors include: quality of life and depressive symptomatology.

4.3 RESEARCH DESIGN AND METHODS

All insulin dependent diabetes mellitus patients seen at Children's Hospital of Pittsburgh from January 1, 1950 to May 31, 1980 formed the sampling frame for inclusion in the EDC. Participants had to meet the following criteria: 1) onset of insulin dependent diabetes mellitus at age 17 years or less; 2) insulin therapy prescribed at discharge; 3) an initial diagnosis, or being seen within one year following diagnosis at Children's Hospital of Pittsburgh; and 4) residence within 100 miles of Pittsburgh or 2.5 hours of driving distance from Pittsburgh. Recruitment and response rates for the EDC study have been detailed extensively in previous publications (Orchard et al., 1990). Six hundred and fifty eight participants completed baseline examinations between 1986 and 1988.

Of the 658 participants enrolled at baseline (1986) for participation in the Pittsburgh Epidemiology of Diabetes Complications Study, 643 were Caucasian and 15 were African American. Thirteen of the African Americans were female participants and 2 were African American males. This sample was epidemiologically representative of the Allegheny County population and the incidence of T1D for that time frame (LaPorte et al., 1986; Orchard et al., 1990; Wagener, Sacks , LaPorte, & Macgregor 1982).

Males composed 51% (n=333) of the total sample. Age range for the males at baseline was from 8.5 years to 47.4 years. The duration of diabetes varied: 13 % (n=44) had diabetes for less than 10 years, 40 %(n=136) had diabetes between 10 and 19 years, 35% (n=117) of the

participants had diabetes between 20 and 29 years and, 11 % (n=36) of the participants had diabetes for 30 years or more. Overall mean for duration of diabetes for all males was 19.5 years (s.d.± 7.6 years).

Because ED is only present in males who have reached an age of sexual maturity, an additional inclusion criterion for the ED study was age greater than or equal to an age of 18 years. Thirty-two of the 333 males were less than 18 years of age and baseline ED status was missing for three participants, therefore, the assessment of prevalent ED was based on a sample size of 298 males. As the 32 males reached 18 years of age they were entered into the risk set for the incidence analysis.

At baseline and all subsequent biennial examinations, participants completed questionnaires and were assessed for potential risk factors and diabetes complication development. Two weeks prior to their examination at the Diabetes Research Center at the University of Pittsburgh, participants were mailed self- report questionnaires that included a medical history, lifestyle questionnaire, assessment of depressive symptoms and containers with detailed instructions for 24 hour urine and overnight specimen collections that were to be brought to the research center the day of the examination (Orchard et al., 1990). Follow-up examinations were conducted every two years and were similar to the baseline examination. Data were then collected biennially, for a period of 10 years (1986-1998). Cycle 1 through Cycle 6 exams took place over a 10-year period and included face-to-face clinic visits, physical assessments, laboratory testing and self report. Collection of data continued after the ten year follow-up with annual surveys, and a full examination at 18 years (Cycle 10:2006-2008) using the above methods.

4.3.1 Measures

ED was used as the **outcome measure** and was defined as a persistent inability to attain and maintain an erection adequate to permit satisfactory sexual performance not due to any other problem as measured by the examining physician while conducting the Diabetes Control and Complications Trial (DCCT) clinical neurological examination protocol. ED was to be present for at least 30 days prior to the examination. Trained physician investigators inquired about autonomic neuropathy symptoms that included questions relating to 1) postural hypotension, 2) gastroparesis, 3) diabetic diarrhea, 4) colonic atony, 5) sudomotor abnormality, 6) hypoglycemic unawareness, and 7) genitourinary autonomic neuropathy symptoms. ED was a "yes or no" determination after genitourinary system review by the examining physician. *Prevalent cases of ED* were those males reporting ED at baseline exam (1986-1988) while *incident cases of ED* were those males who were negative for ED at baseline but developed ED during a follow-up cycle (1989-2007). The cycle in which the participant first reported ED following baseline examination was considered the incident cycle for ED.

4.3.1.1 Demographic Measures

Age was verified and recorded as age in complete years calculated from the participant's self-reported date of birth in month, day, and year. Income, marital status and level of education were all self-reported by the participant on the EDC Lifestyles Questionnaire. *Income* was chosen from 1 of 3 income categories from; 1) $5,000/year to < $15,000, 2) $15,000 to <$30,000 and 3) >$30,000/year. *Marital Status* was measured categorically as follows: 1) never married, 2) married, 3) separated, 4) divorced, 5) widowed, 6) not married, or living with parent. *Highest level of formal education* response was chosen from a list of categorical

response list that included: 1) some high school or high school graduate, 2) some college or received bachelor's degree, or 3) graduate education beyond bachelor's degree.

4.3.1.2 Biologic Measures

Fasting blood samples were used to measure lipids, and HbA1/HbA1c. For the first 18 months of the EDC, *HbA1* was determined by using saline-incubated blood and microcolumn cation exchange chromatography (Iso-Lab). Following the remainder of the 10-year follow-up period, HbA1 was measured by an automated high performance liquid chromatography method (BioRad, Diamat). These two methods were found to be almost identical (r=.95). HbA1's were converted to DCCT aligned HbA1c's for data analysis. The following conversion formula was applied to the first 10 years of HbA1 samples; DCCT HbA1=(0.83xEDC HbA1) + 0.14, while to the second 10 year EDC HbA1c samples the following conversion formula was applied; DCCT HbA1c=(EDC HbA1c-1.13)/0.81)(Prince et al., 2007). Normal range for Hba1 was considered to be <7.3. %. *Duration of diabetes* was calculated from age at diagnosis recorded at baseline and at each biennial visit. Selected and trained research study staff completed the measurement procedure for the *Expiration/Inspiration (E/I) ratio test.* The E/I ratio, an autonomic nervous system function test, was measured with the participant in a supine position, limb ECG leads were attached and a lead II rhythm tracing recorded. The participant was then instructed to inhale deeply for 5 seconds followed by a forced expiration for 5 seconds and to continue this process of deep inspiration and forced expiration every 5 seconds for a total of 2 minutes. The participant was prompted by the examiner for determination of the 5 second intervals and at each prompt the ECG was marked. Both the shortest R-R interval of each inspiration segment and the longest R-R interval of each expiration segment were

measured in milliseconds. The E/I ratio was then calculated using the sum of six of the expiration (EXP) and inspiration (INP) R-R intervals using the following formula; sum of (R-R) EXP/ sum of (R-R) INP. Values < 1.1 were considered indicative of autonomic neuropathy (Stella et al., 2000). There were 10 complications assessed for this analysis. N*umber of complications* was a summation score calculated using the following: CAD, CDSP, LEAD, nephropathy and retinopathy. Score range was from 0-5 with the higher number indicating more complications. Hypertension was assessed separately. AN and SAN were not included in the total number of complications because measurement at baseline was available for only 27% of the male participants (84 without ED and 8 with ED). *Type of complications* were measured as follows; 1) autonomic neuropathy (AN) (confirmatory was an E/I ratio < 1.1 while an E/I ratio > 1.1 was considered negative for AN), 2) Confirmed Symptomatic Autonomic Neuropathy (SAN), an average E/I Ratio of <1.1 and 2 or more of the other autonomic symptoms as determined by the examining physician using the DCCT neuropathy protocol, 3) Distal Symmetrical Polyneuropathy (DSP) using the DCCT protocol the examining physician documented clinically evident diabetic peripheral neuropathy with at least 2 of the following symptoms consistent with DSP; abnormal sensory exam consistent with DSP, or decreased or absent deep tendon reflexes, 4) Confirmed distal symmetrical polyneuropathy (CDSP) was clinically evident diabetic peripheral neuropathy consistent with DSP confirmed by physician's exam and vibratory threshold of >2.39 for ages < 36 years, >2.56 for ages 35-50 years, or >2.89 for ages > 50 years 5) Resting ankle and arm blood pressure readings, using a Doppler Flow Detector, and the participant in the supine position, were used to determine the presence of lower extremity arterial disease (LEAD). Ankle-brachial pressures were calculated using the arm pressure taken closest in time to the ankle pressure. Any participant with an

ankle-brachial index (AB) of <0.8 for any of the four vessels or a history of claudication or of amputation for vascular reasons was considered positive for LEAD, 6) Overt nephropathy (ON) was an albumin excretion rate >200micrograms/min in multiple timed urine specimens, renal dialysis or a kidney transplant. Data for ON were coded none (0), or overt or renal failure (1), 7) Coronary artery disease (CAD) documented as positive if the participant had a history of MI (confirmed by ECG-Q-waves or hospital records, using standardized criteria), coronary arterial occlusion (>=50% occlusion by angiography, myocardial infarction (Minnesota codes 1.1, 1.2), ischemic ECG (Minnesota codes 1.3, 4.1-4.3, 5.1-5.3 or 7.1) or revascularization at the 10 year-examination, or diagnosis of angina by the EDC study physician during any cycle (Prince et al., 2007)), 8) Cerebral Vascular Disease (CBVD) was positive if there was a history of a stroke, 9) retinopathy was determined from fundus photography and measured as none (0), retinopathy and/or laser treatment of retinopathy (1), 10). Hypertension was defined as a blood pressure greater than 140/90 mmHg or on anti-hypertensive medication. *Systolic and Diastolic blood pressure* was measured per Hypertension Detection and Follow-up Protocol using a random zero sphygmomanometer. Mean of the second and third blood pressure readings were used and entered as a continuous variable for systolic and diastolic pressures separately. Participants were asked to self-report medication used for hypertension. To qualify as a *anti-hypertensive medication* the medication had to be used to treat hypertension in the participant Use of Angiotensin II receptor blockers (ACE-MED) as well as lipid lowering medication were also separately self-reported by the participant using the EDC Medical History Form. The *lipid profile*s were measurements for HDL and nonHDL cholesterol. HDL was determined by means of precipitation (heparin-manganese chloride method) (Warnick & Albers, 1978). Triglycerides (Bucolo & David, 1973)

as well as plasma cholesterol were measured enzymatically (Allain et al., 1974). Low density lipoproteins (LDL) were determined from measurements of the total cholesterol, triglycerides, and HDL measurements using the Friedewald formula (Friedewald et al., 1972). For this analysis, non-HDL cholesterol was calculated as Total cholesterol minus HDL.

4.3.1.3 Lifestyle Behavioral Factors

Smoking status was in response to "Have you ever smoked at least 100 cigarettes in your lifetime?" *Total alcohol* was self-reported by the participant. The following question was asked "How often do you drink the following beverages (Beer-12oz, wine-4oz, mixed drinks/liquor)? and how much of each beverage do you usually drink on a weekly basis?" Both of these measures were part of the self-reported survey questions from the EDC General Medical History Questionnaire. This questionnaire was also mailed two weeks prior to the scheduled EDC for review at the time of the scheduled visit. In addition to the total number of alcoholic beverages per week, total alcohol was categorized into the following; no average weekly intake of alcoholic beverages (0), 1-3 drinks per day (1), or greater than 3 drinks per day (2).

4.3.1.4 Psychosocial Measures

Depressive symptomatology was measured by the Beck Depression Inventory (BDI-II). High scores (ranging from 29 to 63) were suggestive of severe depressive symptomatology. Scores ranging from 20 to 28 indicated moderate depressive symptomatology whereas scores ranging from 14 to 19 indicated mild depressive symptomatology. Those with total scores between 0 and 13 were considered to be without clinical depressive symptomatology (Beck, 1961). The BDI-II was part of the EDC Lifestyle Questionnaire. Participants were mailed this

questionnaire two weeks prior to their EDC visit and returned the survey at the time of their EDC clinical examination.

Also by self-report, on the EDC Lifestyle Questionnaire *quality of life* was assessed by a modified version of Diabetes Control and Complications Trial Quality Of Life (DCCT-QOL) instrument. The DCCT-QOL was developed for use in the Diabetes Control and Complications Trial (DCCT) to compare the relative personal burden for participation in either the intense treatment group or standard care group for diabetes management. It was divided into four domains that included the following domains; impact (20 questions), worry: social/vocational (7 questions), worry: diabetes related (4 questions) and satisfaction (15 questions) (Group, 1988). Responses to questions within each of these domains were made with a 5- point Likert scale. Impact and worry scales were from 1 (no impact and never worried) to 5 (always impacted and always worried). Impact total scores ranged from 14-70. Worry total score ranged from 11-66. The higher scores indicating more impact and worry. Satisfaction was surveyed using 3 general questions: one question responses were very satisfied, fairly satisfied, or, not very satisfied. Scores for this question ranged from “very satisfied "(1) to "not very satisfied"(3). The other 2 questions, questions of comparison for general health compared to other persons their age with and without diabetes, were scored using a Likert scale from 1 (excellent health) to 4 (poor health). Total score range for satisfaction was from 3-11, the higher score indicating less satisfaction. Total m DCCT-QOL scores ranged from 28-147, higher scores indicating more impact and worry from diabetes and less satisfaction with the quality of life. In addition to the total mDCCT-QOL score and the domain scores there was one question within the impact domain that was reviewed separately for this study. This question “How often does your diabetes interfere with your sex life” was

answered on a Likert scale from 1-5, 1 being never to 5 being all the time. Scores for this question ranged from 1-5, higher score indicating more interference.

4.3.2 Statistical Analysis

Analysis was performed using SAS (Version 9.1.3 SAS Institute Inc., Cary, NC). All data were verified after an extensive detailed exploratory analysis to assess missing values and outliers. Descriptive statistics were generated for the continuous variables and normality was determined for each of these variables. For normally distributed variables the Student's t-test was used to assess case and control differences while for those non-normally distributed variables the Kruskal-Wallis Test were used. Chi-square test for binomial proportions was used to test differences for the categorical variables. Tests for trend were completed using the Cochran Armitage test for trend. P-value was set at 0.05 to indicate statistical significance. Logistic regression was used to determine prevalent predictor variables for the prevalent model controlling for duration of diabetes, while Cox proportional hazards regression was used to examine the independent association between time to ED incidence and the baseline predictor variables. The logistic regression model for the psychosocial variables was adjusted by duration of diabetes and total number of complications. Stepwise selection was used for Model determination. The Wald chi-square test statistic was used to test each of the predictor variables and variables were selected if $p< 0.05$. Age-specific prevalence rates were calculated from total sample of males within the specific age category and confidence intervals were calculated for each age-specific group. Incident cases were defined as a case when first

documented by the examining physician. Cumulative Incidence Rates were calculated by Kaplan-Meier method. Incidence density was calculated by dividing the number of participants developing a first event by the person years of observation for those at risk during the study. One multivariate outlier was identified in the dataset and was subsequently deleted from the analysis; therefore, the total number of males enrolled at baseline and used for this analysis totaled 332.

4.4 RESULTS

4.4.1 Baseline Characteristics of Males Enrolled in the EDC

One multivariate outlier was identified in the dataset and was subsequently deleted from the analysis; therefore, the total number of males enrolled at baseline and used for this analysis was 332. The following characteristics of all males enrolled in the EDC at baseline (N=332) included: mean age 27.53 ± 7.78 years (range 8.47-47.43 years), duration of diabetes 19.55±7.46 years, systolic blood pressure 117.49 ± 17.14 mmHg, diastolic blood pressure 75.52 ± 11.20 mmHg, mean glycosylated hemoglobin 8.74 ± 1.45%, BMI 23.59 ± 3.1 kg/m^2 , high density lipoprotein 48.61 ± 9.73 mg/dl, and non-HDL cholesterol 140.69 ± 44.56 mg/dl. (Refer to Table 4.1).

Prevalence: Of the 332 male participants enrolled in the EDC, 32 (9. 6%) were eliminated from the baseline analysis due to age less than 18 years, and 3 (0.9%) had missing ED status data. Thirty-one male participants (10.4%) were identified as prevalent ED cases. The prevalence of ED rose from 2% in those 18-29 years of age to 42% in those 40-45 years of

age (test of trend $p < .05$) and this relationship is graphically shown in Figure 1. Sixty-one percent of the total ED cases (19/31) occurred in the males with ages between 30 and 39 years. Refer to Table 4.1 and Figure 4.1

Table 4.1 Age specific Prevalence Rates for Males Enrolled in the EDC at Baseline (1986-1988)

Age	ED+	Number of males withi age-group	% within age group with ED	95% Confidence Interval
18-29 years	4	172	2	(0.08-4.58)
30-39 years	19	107	18	(10.52-25.00)
40-45 years	8	19	42	(19.9-64.31)
Total	31	298	10.4	(6.93-13.87)

With increasing duration of diabetes, the prevalence of ED also rose. Nineteen percent of the cases (n=6) occurred with a diabetes duration between 10 and 20 years, with the first case being reported after 10.7 years diabetes duration. Sixteen percent of the ED cases (n=5) occurred after 21-25 years of diabetes duration, 35% (n=11) occurred after 26-30 years duration while 29% (n=9) of the cases occurred after 31-37 years duration.

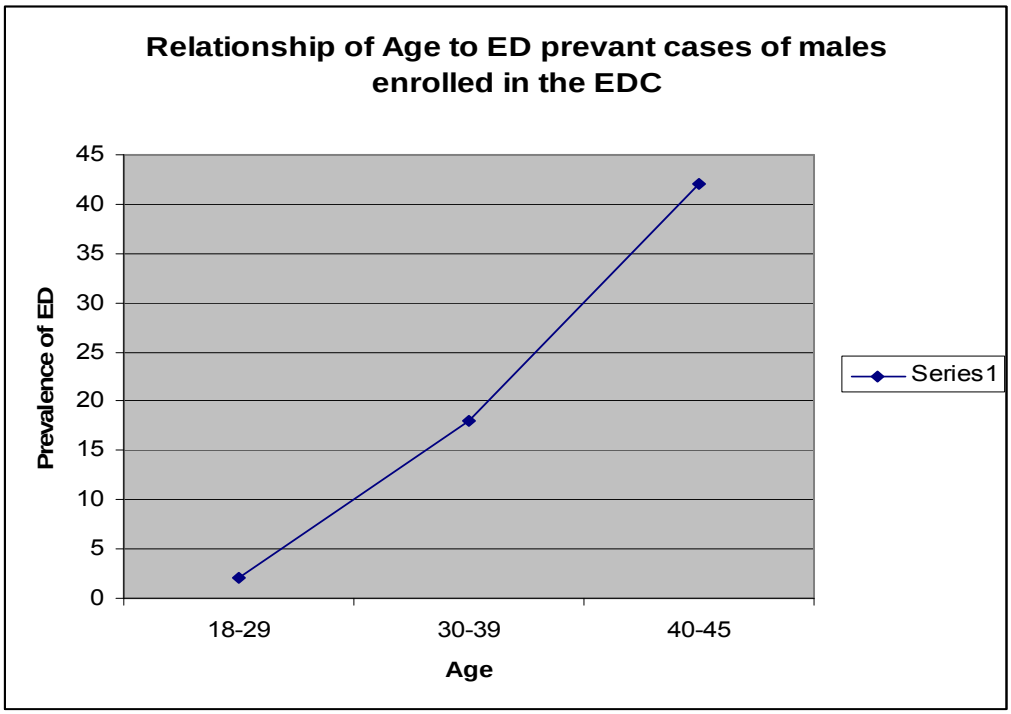


Figure 4.1:The relationship of age to ED prevalence by baseline EDC exam (1986-1988)

Mean age of the males with ED was 35.8 ± 5.3 years and mean duration of diabetes was 26.9±5.9years. Cases were significantly different from those without ED for baseline characteristics of age, duration of diabetes, systolic blood pressure, diastolic blood pressure, BDI score, BMI, marital status, CAD and hypertensive status. Males with ED were older, had a longer duration of diabetes, had higher systolic and diastolic blood pressures, and had 3.21 (95% C.I. 1.4-6.6, p=0.0021) and 3.8 (95% CI 1.45-9.96, p=0.0106) times the odds to have hypertension and CAD respectively, than those males without ED. Males with ED did not significantly differ from males without ED in the baseline characteristics of metabolic control (HBA1), level of education, income, or the current use of ace or lipid lowering medication. (Refer to Table 4.2. However, males with ED had 6.27 (95% CI 2.12-10.18) times and 4.65

(95% CI 2.12-10.18,) times the odds to have proliferative retinopathy and overt nephropathy respectively than those males without ED.

Table 4.2 Baseline Characteristics of the all EDC male participants (N=332)

	Total (N=332)	Without ED (n=266)	With ED(+) (n=31)	*p value
Age (m±sd) years	27.53±7.78 Range: 8.47-47.43	28.2 (± 6.4) Range: 18.01-47.43	35.8 (±5.3) Range: 22.9-44.88	* p<0.0001
Duration(m±sd) years	19.55±7.46 Range: 7.69-37.40	19.9 (± 6.8) Range: 8.1-37.4	26.9 (±5.9) Range:10.07-35.91	*p<0.0001
Age at onset of diabetes (m±sd) years	8.34 ± 4.17	8.27 ± 8.3 Range:0.79-15.56	8.92 ± 3.7 Range: 1.63-15.58	p>0.05
DCCT HbA1c(m±sd) %	8.74 ±1.45	8.72 (±1.41) Range:6.19-13.58 n=265	8.94 (±1.77) Range:5.28-12.09 n=30	p=0.427
SBP(m±sd) mmHg	117.49±17.14 Range: 76-234	117.9 (±16.7) Range: 92-234	126.4 (± 22.2) Range:76-188	*p=0.007
DBP(m±sd) mmHg	75.52±11.20 Range: 44-118	77.9 (± 10.8) Range:45-118	79.8 (± 12.2) Range:49-102	*p =0.033
BMI(m±sd)	23.59±3.1 Range: 13.87-33.12	24.1 (± 2.8) Range: 17.32-33.12 n=265	22.9 (± 2.2) Range: 19.4-26.4	*p=0.03
WHR(m±sd)	0.87±0.053 Range: 0.75-1.1	0.88 (± 0.05) Range: 0.75-1.10	0.89 (±0.04) Range: 0.81-0.99	*p=0.011
MARITAL STATUS (n,% total) **1=never married** **2=married** **3=separated** **4=divorced** **5=widowed** **6=not married, living with partner**	 175 (52.55) 131 (39.34) 2 (0.6) 18 (5.41) 0 7 (2.10)	 138 (46.3%) 109 (36.6%)= 1 (0.34%) 13 (4.4%) 0 6 (2.01%)	 5 (16.13) 20 (64.52) 1 (3.23) 0 (0.00) 5 (16.13) 0 (0.00)	*p<.0.0001
LEVEL OF EDUCATION (n,% total) **1= SomeHS/HS graduate** **2=Some College** **3=Graduate**	 118 (39.46) 154 (51.51) 27 (9.03)	 100 (38.03%) 139 (52.85) 24 (9.13)	 13 (43.33) 14 (46.66) 3 (10)	p=0.37
INCOME (% total) **1=<$5,000-$15,000** **2=$15,000-$30,000** **3= >$30,000**	 1=26.12 2=38.05 3=35.82	 57 (23.7%) 80 (33.3%) 77 (32%)	 6 (2.5%) 11 (4.6%) 10 (4.2%)	p=0.59

Table 4.2 continued

Smoking Ever(n,% total) **no** **yes**	190(59.01) 132(40.99)	152 (58.91) 106 (41.09).	10 (32.26) 21 (67.74	p=.007
Smoking Now(n.% total) **no** **1es**	50(40) 75(60)	41 (40.59) 1=60 (59.41)	6 (30) 14 (70)	p=.46
Total alcohol (Average /wk)	6.17 ± 11.1 Range:0-53	5.66 ± 8.04 Range: 0-42	10.55 ± 25. 6 Range: 0-53	p=0.33
HDL	48.61 ± 9.73	49 ± 9.7 n=263	44 ± 9.6 n=30	*p=0.006
Non-HDL Cholesterol	140. 69 ± 44.56	142 ± 25 n=263	166.67 ± 47.39 n=30	*p=0.028
CAD (n, % total) **no** **yes**	305 (91.59) 28 (8.41)	248 (92.88) 19 (7.12)	24 (77.42) 7 (22.58)	*p=.0106 (Fisher Exact)
+AN (n, % total) **no** **yes**	60(65.22) 32(34.78) n=92	57 (67.86) 27 (32.14) n=84	3 (37.5) 5 (62.5) n=8	p=.12 (Fisher Exact)
+Symptomatic Autonomic Neuropathy (n, % Total) **no** **yes**	83 (90.22) 9 (9.78)	79 (94.04) 5 (5.95)	4 (50) 4 (50)	p=.0026(Fisher Exact)
Hypertensive (n,% total) **no** **yes**	268(80.72) 64(19.28)	215 (80.83) 51 (19.17) n=266	18 (58.06) 13 (41.94) n=31	*p=.0092
Overt Nephropathy (n, % total) **no** **yes**	238 (71.47) 95 (28.52	192 (71.91) 75 (28.09)	11 (35.46) 20 (64.52)	p< .0001
Lower Extremity Arterial Disease (n, % total) **no** **yes**	308(93.05) 23 (6.95)	250 (93.63) 17 (6.37)	25 (80.65) 6 (19.35.)	p=0.0217
Proliferative Retinopathy **no** **yes**	219 (67.18) 107 (32.82)	181 (68.56) 83 (31.44)	8 (25.81) 23 (74.19)	p<.0001

Table 4.2 continued

Cerebral vascular Disease (n, % total) **no** **es**	331 (99.4) 1 (0.3)	265 (99.62) 1 (0.38)	31(100) 0 (0)	p=1 (Fisher exact)
Confirmed Distal Symmetrical Polyneuropathy **no** **yes**	230 (69.27) 102 (30.73)	192 (71.91) 75 (28.09)	5 (16.13) 26 (83.87)	p<.0001 (Fisher Exact)
Distal Symmetrical Polyneuropathy **no** **yes**	227 (68.37) 105 (31.63)	189 (70.79) 78 (29.21)	5 (16.13) 26 (83.87)	p<.0001 (Fisher Exact)
Total Complications	1.18 ± 1.35	1.01(14.64 have 3 or more complications)	2.56(58% with 3 or more complications)	p<.0001(test for trend)
Ace Medication (n, % total) **no** **yes**	307 (96.54) 11 (3.46)	247 (96.86) 8 (3.14) n=255	27 (90.) 3 (10) n=30	p=0.0972 (Fisher Exact)
Lipid Medication (n, % total) **no** **yes**	317 (99.37) 2 (0.63)	255 (99.61) 1 (0.39)	29 (96.67) 1 (3.33)	p=.1991(Fisher Exact)
Blood Pressure Medication **no** **yes**	257 (90.49) 27 (9.51)	233 (91.73) 21 (8.27)	24 (80) 6 (20)	p=.0496 (Fisher Exact)
QOL(m ± sd)	52.72 ± 12.19 Range: 33-129	52.2 ± 12.1 Range:33-129	57.4 ± 11.5 Range: 36-81	*p=0.007
Impact (m ± sd)	30.00 ± 6.75 Range: 19-53	29.44 ± 6.1 Range: 19-52	34.72 ± 7.94 Range:23-53	*p=0.0003
Worry(m ± sd)	16.41± 6.42 Range:1-44	16.55 ± 6.5 Range: 1-44	15.3 ± 5.78 Range:6-25	p=0.44
Satisfaction(m ± sd)	5.99 ± 1.96 Range: 3-11	5.83 ± 1.93 Range: 3-11	7.37 ± 1.65 Range: 4-10	*p<0.0001
Sex Question (m ± sd)	1.72 ± 1.10 Range: 1-5	1.54 ± 0.78 Range: 1-5	3.3 ± 1.4 Range: 1-5	*p<0.0001
BECK(mean±standard deviation)	6.2±6.20 Range:0-32	5.8 (± 5.7) Range: 0-30 n=232	10.6 (± 8.4) Range: 0-32 n=27	*p=0.003

Men with ED had 3.15 times the odds to report ever smoking (95% CI 1.43-6.95, p=.007), 1.6 times to report current smoking (95% CI 0.57-4.51, p=.46) and consume more alcoholic drinks per week than those males without ED. Mean BDI score (10.6 (± 8.4) p=.0003), although not suggestive of depressive symptomatology, and total QOL score (57.4 ± 11.5 p=.007) were higher in males with ED. More impact (p=.0003) from diabetes and more interference as a result of diabetes on their sex life (p<.0001) were also reported in the males with ED. HDL and nonHDL cholesterol was significantly different between those with ED and those without ED. Males with ED had lower mean HDL (44 ± 9.6, p=.006) and higher nonHDL (166.67 ± 47.39, p=.028) cholesterol.

Those factors found to be related to ED univariately included: duration of diabetes, systolic and diastolic blood pressure, BMI, HDL, nonHDL cholesterol, HbA1 (DCCT adjusted), hypertension, CDSP, LEAD, CAD, retinopathy, nephropathy, smoking ever, marital status, ace medication, lipid medication and blood pressure medication. Those variables not showing univariate significance included level of income, age of onset of diabetes, level of education, and total alcohol. After controlling for duration of diabetes, Model 1[ED (-) n=246, ED (+) n=29] had CDSP and HDL cholesterol as the predictor variables for ED (Hosmer and Lemeshow Goodness of Fit Chi-Square= 10.2868, df=8, p=.2455). Model 2[ED(-) n=231, ED(+) n = 27), adjusted for duration of diabetes and total complications, resulted in the model with total BDI score as the predictor variable(Hosmer and Lemeshow goodness of fit Chi-Square=5.9491, df=8, p=.6529). By Cycle 10 (2004), 70 males had died; 15 (21.4%) were prevalent cases. Log-rank test for equality (15 males with prevalent ED vs. 55 males without ED of all males who died) over the strata, shows that these two curves were different, log-rank Chi square=15.0830, df=1, p=.0001.

4.4.2 Incident Characteristics of Males with ED

In Cycles 2 through 6 and Cycle 10 there were 54 new cases identified for ED (refer to Table 4.3). The incidence analysis was based on 53 cases. There were no incident cases identified in Cycle 7 and 2 cases identified in Cycle 8. Because these two cycles were sub-studies within the EDC and did not include all participants enrolled, they were not included in this analysis. Mean follow-up time in years for the 181 males who never developed ED was 9.8 years whereas mean follow up time for the males with incident ED was 10.9 years. Follow-up time was calculated by summing only those years in which ED data was documented, thereby accounting for missing cycles not seen. After bivariate analysis,for time of the ED event mean age for the incident cases was 40.61± 5.9 (range 26.7-60.8) years (Refer to Table 4.4) while the mean duration of diabetes was 32.54 ± 5.88 (range 20.9-51-9) years (Refer to Table 4.5). Mean systolic and diastolic blood pressures were 125.29 ± 20.56 (range 88.0-191.0) mmHg and 75.57 ± 11.36 (range 49.0-108.0) mmHg, respectively. Mean HbA1 was 10.68 ± 2.19%. The mean E/I ratio for these incident males was 1.14 ± 0.122 (range 1.0-1.55) and mean BDI total score was 9.5 ± 6.9 (range 0-32). Refer to Table 4.6. Crude incidence rate for this cohort was 17.78% [53 (number of new cases developing ED over 16 years follow-up)/298 (number at risk from baseline without ED)] and person time at risk was 2034 person years. The incident rate was 2.60/ 100/year. By Cycle 10, cumulative hazard was 0.561 (Refer to Table 4.7). Ninety percent of the incidence cases were between 30 and 49 years of age. Refer to Table 4.4 and Figure 4.2.

Table 4.3 New ED Cases by Cycle 2 thru 6(1988-1998) and Cycle 10 (2004-2007)

cycle	2 1988-1990 n=251	3 1990-1992 n=225	4 1992-1994 n=205	5 1994-1996 n=176	6 1996-1998 n=205	10 2004-2007 n=67
Number of new ED cases	6 (11%)	6 (11%)	10 (19%)(	9 (17%)	14 (27%)	8 (15%)

Table 4.4 Age distribution of the 53 Incidence Cases at time of ED event

	n	% total
20-29 years of age	2	3.7
30-39 years of age	21	**38.9**
40-49 years of age	27	**51.8**
50-59 years of age	2	3.7
60 + years of age	1	1.9
total	53	100

The males were 2 times more likely to have developed ED after duration of diabetes longer than 30.1 years. (Refer to Table 4.5)

Table 4.5 Duration Distribution of the Incident Cases

Duration (Years)	n	% of total
20-25	8	14.8
25.1-30	10	18.5
30.1-35	18	33.3
35.1-40	14	25.9
40 +	4	7.5

At the time of the ED event, only 38 % of the incident cases documented taking an ACE medication while 4.4 % noted taking a lipid lowering medication. Males who were married were more likely to report ED (67.92%, n= 36) than those males who were never married (20.75%, n=11). Seventy three percent had some college through a professional degree (n=38) while almost half of the males reported a yearly income greater than $30,000. Incident ED was associated with positive history of confirmed distal symmetrical polyneuropathy (64.10%, n=25), and proliferative retinopathy (73.58%, n=39). (Refer to Table4.6) Approximately 50% (n=23) were hypertensive. In the multivariate analysis, controlling for duration of diabetes, the significant variables of the demographic, biologic and lifestyle behavior variables entered associated with ED incidence were confirmed distal symmetrical polyneuropathy and nonHDL cholesterol. From the multivariate model with the psychosocial variables, after controlling for duration of diabetes and for number of complications was the total BDI score. Refer to Tables 4.6 and Table 4.8 and Table 4.9).

Table 4.6 Characteristics of the 53 Incident Cases at time of ED event (1988-2007)

Age (m±sd) years	40 ± 5.96 Range: 26.27-60.90
Duration of Diabetes (m±sd) years	32.54 ± 5.94 Range: 20.9-51.90
Marital Status:	69.23 % n=36 married
Level of Education	74.5% n=38 college/ graduate / professional)
Income	38% (n=19) annual income < $30,000
HbA1	10.68 (m±sd) 2.19 Range:7.4-17
Systolic Blood Pressure	125 (m±sd) 20.71 Range: 88-191
Diastolic Blood Pressure	76.10 (m±sd) 10.82 Range: 52-108
E/I Ratio	1.138 (m±sd) .123 Range: 1-1.545
CDSP	63.16% n=24
Proliferative Retinopathy	73.08% n=38
Overt Nephropathy	45.28% n=24
Hypertension	48.89% n=22
Taking Ace Medication	38.46% n=20
Taking Lipid Medication	4.55% n=2
BECK	9.34 (m±sd) 6.95 Range: 0-32
Age Categories (years)	<30 years n=2 (4%) 31-40 years n=21 (40%) 41-50 years n=27 (50%) 51-61 years n=3 (6%)

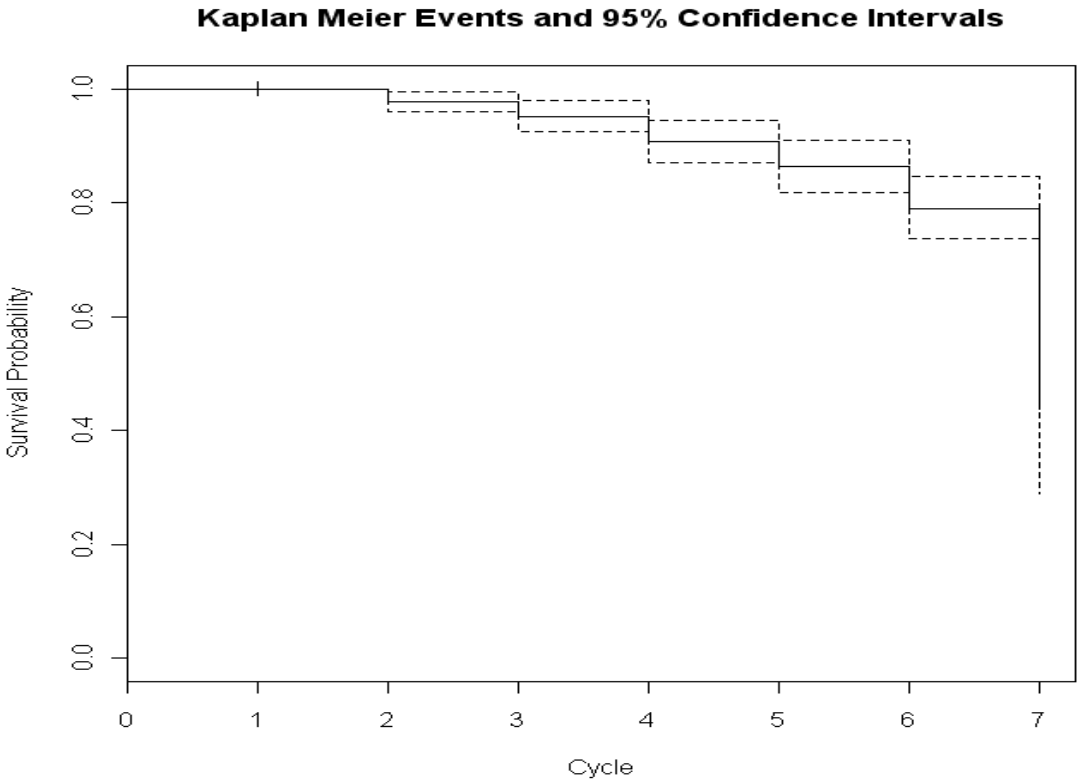


Figure 4.2 Kaplan Meier 53 Incident Cases by Cycle

Table 4.7 Kaplan-Meier Table 53 Incident cases by Cycle

Cycle	# at Risk	#of Events	Survival Probability	Standard Error	95% CI (Survival probability)
2	263	6	.977	.0092	.959-.995
3	232	6	.952	.0136	.926-.979
4	210	10	.907	.0190	.87-.945
5	185	9	.862	.0231	.818-.909
6	165	14	.789	.0282	.736-.847
10	18	8	.439	.0938	.288-.667

Table 4.8 Cox proportional Hazards (Relative Risk) for all baseline risk factors

Variable	Parameter Estimate	Standard Error	p-value	Hazard Ratio	95% CI
HbA1 %	.1675	.0987	.0897	1.182	.974-1.435
Duration of Diabetes years	.1039	.0185	<.0001	1.109	1.07-1.150
Age years	.1138	.0203	<.001	1.121	1.077-1.166
Systolic Blood Pressure mmHg	.1078	.0091	.0513	1.018	1-1.036
Diastolic Blood Pressure mmHg	.0362	.01349	.0073	1.037	1.01-1.065
BMI	-.0014	.0042	.7391	.999	.99-1.007
BDI	-.01738	.00701	.0131	.983	.969-.996
Height (cm)	.01032	.01768	.5595	1.01	.976-1.041
Weight (kgms)	.02471	.01165	.0338	1.025	1.002-1.049
Total Alcohol	-.02390	.02601	.3581	.976	.928-1.027
Total Insulin Units	-.00282	.00247	.2529	.997	.992-1.002
Total Cholesterol	.01247	.0028	<.001	1.03	1.007-1.008
Triglycerides ≤130 >130	.47636	.2963	.1079	1.610	.901-2.878
HDL ≥45 <45	.52734	.38653	.125	1.694	.79-3.694
HDL	-.02294	.01599	.1594	.977	.947-1.008
Triglycerides	.00373	.00161	.0207	1.004	1.001-1.007
nonHDL	.01349	.00275	.<.0001	1.014	1.008-1.019
LDL	.01724	.00346	<.001	1.017	1.00-1.024
impact	.05235	.02156	.0135	1.055	1.011-1.1
worry	.01551	.02240	.4885	1.016	.972-1.061
Satisfaction	.23418	.07803	.0027	1.264	1.085-1.473
Sex Question	.2767	.1569	.0777	1.319	.970-1.793
QOL	.02413	.0124	.0468	1.024	1-1.049

Table 4.8 continue-

Ever smoked	-.0475	.10099	.6383	.954	.782-1.62
Level of Education	.0986	.1882	.6006	1.104	.763-1.596
Income	-.12653	.03637	.0451	.881	.77-.998
Marital Status	.9686	.2776	.0005	2.634	1.529-4.538
Age of Onset of Diabetes	-.0285	.03325	.3906	972	.919-1.037
Lipid Med	.3988	1.029	.6982	1.49	.998-11.188
Ace Med	.3372	.17042	.0478	1.401	1.003-1.957
CDSP	1.1639	.28014	<.001	3.202	1.849-5.545
Overt Nephropathy	1.0169	.28210	.0003	2.765	1.59-4.806
Proliferative Retinopathy	1.0409	.2758	.0002	2.832	1.649-4.861
CAD	.82603	.43412	.0571	2.284	.975-5.349
LEAD	.14152	.5217	.7862	1.152	.414-3.203
SAN	-.00582	.36329	.9872	.994	.488-2.026

Table 4.9 Multivariate Final Cox Model with Independent Predictors for ED (53 Incident Cases)

Variable	Parameter Estimate	Standard Error	p-value	Hazard Ratio	95% CI Hazard Ratio
Duration of Diabetes	0.09066	0.02294	<0.001	1.095	1.047-1.145
CDSP	0.82875	0.30352	0.0063	2.290	1.263-4.152
nonHDL	0.01344	0.00322	<0.001	1.014	1.007-1.020
Weight	0.02855	0.0124	0.0450	1.029	1.001-1.058

4.5 DISCUSSION

Prevalent ED as ascertained by physician exam in the Pittsburgh-EDC population was 10.4%. As age increased, the prevalence of ED also increased. The prevalence of ED rose from 2% in those 18-29 years of age to 42% in those 40-45 years of age. Sixty-one percent of the total ED cases (19/31) occurred in the males with ages between 30 and 39 years. After entering all of the demographic, biologic, lifestyle behavior and use of antihypertensive medication variables into a multivariate logistic regression model, controlling for duration of diabetes, only biologic variables of CDSP and HDL were identified as independent associated risk factors for ED. In the multivariate logistic regression model with the psychosocial variables entered, after controlling for duration of diabetes and total number of complications, the mean BDI symptomatology score was the significant independent associated risk factor of ED identified.

Incidence was 17.78 % from 1989 to 2007 and reflects 53 new cases of ED. Person time at risk was 2034 person years over 18 years; the incident rate per year was estimated at 2.6/100 /year. Ninety-five percent of the incident cases were between 30 and 49 years of age. After entering all of the demographic, biologic, lifestyle behavior and use of anti-

hypertensive medication variables into a multivariate Cox model (n=53), controlling for duration of diabetes, only the biologic variables of CDSP, nonHDL and weight were identified as the independent predictors for ED. In the multivariate Cox model with the psychosocial variables entered for the incident cases (n=53), after controlling for duration of diabetes and total number of complications, the mean BDI symptomatology score was the significant independent predictor of ED identified.

Both the prevalent and incident cases of ED had CDSP, lipid sub-fractions and BDI score as independent predictors of ED. The multivariate Cox (incidence) model also identified weight as an independent predictor.

This prevalence rate was somewhat lower than previously reported (20%-90%) in the literature for ED and all types of diabetes(Bacon et al., 2002; Bacon et al., 2003; http://www.diabetes.org/diabetes-statistics/complications.jsp, 2007; A Vinik et al., 2003). Our reported incidence rate of 17.78 % was also lower than previously reported for studies of males with T1D by Klein (Klein et al., 2005) at 25.6% and McCulloch (McCulloch, Young, Prescott, & Campbell, 1984) at 28%. Differences found in rates reported across studies may be due to differences in definitions used for ED as well as ascertainment measures. Choice of the measure can affect the sensitivity and specificity. For example, Klein et al (Klein et al., 1996), used particpant self-report to ascertain cases. Males were asked to self- report ED by answering the following question *"Has diabetes caused impotence that is an inability to achieve a normal erection*(Klein et al., 1996)*?"* Participants in this study might have over-reported impotence in that in replying yes to the question posed, they did not rule out other potential interactions between diabetes and/or other comorbidity treatment regimes. Several studies also have reported rates from specialty

clinics (urology) and this higher representation may be the result of males with T1D presenting with more illness and hence are they are more sick than those represented in follow-up for a longitudinal cohort such as the EDC. Our studied used the DCCT neurology criteria and the physician ruled out whether the ED was caused by diabetes. Also the definition and measure used to determine ED varied across studies. Some of the studies have used measures specific for ED such as the International Index (Fedele, 1998) or structured interviews detailing prescence, and severity of the ED, while others have used more objective measures such as nocturnal penile tumescence and rigidity testing. Therefore the research methodology can not be ruled out as a factor affecting these rates.

Several studies have confirmed the association of duration of diabetes and ED (Bacon et al., 2003; Klein et al., 1996; Kloner, 2008a). Longer duration of diabetes was related to ED and found to be an independent predictor in this EDC population. The first case for the prevalent ED cases was after 10.7 years whereas the first case for the incident cases was 20.4 years. This confers with similar findings previously reported (Burnett, 2006; Fedele, 1998; Fedele et al., 2001; Klein et al., 2005). Diabetes is thought to be an age accelerating disease due to the effects of the diabetes disease process on endothelial function at the cellular level. The longer therefore someone has diabetes the faster they are aging. For those with diabetes this may be the reason ED is seen 10 to 15 years earlier than in the general population.

After adjusting by duration of diabetes, HDL cholesterol, in the prevalent cases, and nonHDL cholesterol for the incident cases were significant predictors. Although ED has causal neuropathic pathways , there are also most probably vascular pathologies associated with its development (A. D. Seftel et al., 2004) as well. Higher levels of non-HDL have been associated with endothelial dysfunction and vascular aging (Thomas et al., 2008).

Hypercholesterolemia has been associated with impairment of endoththieum dependent relaxation in smooth muscle cells of the corpus cavernosum (DeBerardis et al., 2007). Impaired endothelial dysfunction results from the modification of the nonHDL cholesterol by glycation, as in those with diabetes, oxidation or incorporation into immune complexes which contribute to vascular smooth muscle and endothelial dysfunction (Ross, 1999). In the prevalent cases HDL cholesterol was a predictor and was noted to be significantly lower than the males without ED. This association may be the resultant effect from vascular stiffness and atherosclerosis development. These abnormal lipid levels may be the common pathway for ED as well as the other macrovascular complications frequently seen in diabetes.

In both the prevalent and incident cases, confirmed distal symmetrical polyneuropathy was found to be a significant predictor of ED. This has been previously reported (Fedele, 1998; Klein et al., 2005; Saigal, Wessels, Pace, Schonlau, & Wilt 2006). Klein et al (Klein et al., 1996) found a relationship between lower extremity pain on ambulation and incident ererctile dysfunction in a 1996 prevalence study from Southern Wisconsin in a group of youth-onset diabets males. The effect of repeated hyperglycemia causes endoneuronal microangipathic change within all sensory nerves which then proceeds to the loss of nerve fibers, especially in the lower extremities and trunk (Yagihashi, 2007). Further, this then causes a decrease in the small skin fibers affecting skin sensativity to stimuli. All of the above therefore contribute to the development of ED in males with T1D.

Finally, the psychosocial predictor variable, BDI total score, found in this analysis for both prevalence and incidence has previously been reported as well. It is unknown however, if ED was caused by the depression or whether the depression was concurrently present as a result of another disease process.

4.5.1 Limitations

There are several limitations to this study. First, the methodology utilized the physician self-reported ED on physical examination. There were no objective findings to concur with this diagnosis and hence it is not known if this was under/over reported. This population was almost all Caucasian, so it is unknown if this statistics hold true for other racial populations. The prevalence analysis was on all males that were enrolled at baseline; however, the incidence data was affected by censoring which further limits the generalizability of these results.

4.5.2 Implications for Future Research

Prospective studies should evaluate the effect of early treatment and intervention to prevent sensory polyneuropathy, control of blood lipids, and depression using standardized objective measures specific to ED. Quality of life should be evaluated using a sexual function specific evaluation tool. Since glycemic control has been shown previously to delay ED from occurring, the self-management and risk perceptions of males with respect to ED should be explored with respect to their knowledge of diabetes, self-efficacy and perceptions of severity for complication development.

5.0 MANUSCRIPT TWO

5.1 ABSTRACT

OBJECTIVE: The purpose of this study was to identify the sequence to the development of ED in relation to other markers of neuropathy, i.e., E/I Ratio, Confirmed Distal Symmetrical Polyneuropathy (CDSP), and Symptomatic Autonomic Neuropathy (SAN).

RESEARCH DESIGN AND ME THODS: From 1989 to 2007, male participants (n=333) enrolled in the Pittsburgh Epidemiology of Diabetes Complication Study (EDC), received biennial examinations in the EDC center and were assessed for potential risk factors and diabetes complication development. In addition to the physical assessment that included autonomic neuropathy review, and distal symmetrical polyneuropathy reviews, E/I ratios were completed on all participants. Fifty-four incident cases of ED were identified during the 18 year follow-up. ED incident cases were identified for E/I Ratio, CDSP and SAN, the cycle in which the ED case was reported and the cycle preceding the incident cycle. Inclusion in this study also included an age greater than or equal to 18 years. Cox proportional Hazard modeling and repeated measure assessment were used to determine independent predictors of ED at the time of reported incident ED and the cycle preceding this report.

RESULTS: Fifty-three incident cases were identified for ED. In the Cox proportional hazards regression model, E/I Ratio [hazard ratio=0.008 (95% CI: 0.001-.0101) , p=0.0002] was significant at the time of the event, but not in the preceding event cycle [hazard ratio=0.312 (95% CI: 0.056-1.75), p=0.1836] ; CDSP [hazard ratio=3.60 (95% CI: 2.01-6.47), p<0.001] was significant in the preceding cycle to ED development and at the time of the event [hazard ratio=4.28 (95% CI: 2.41-7.6), p<.001]. For the repeated measure analysis, CDSP was significant in the preceding cycle to the ED development but not at the time of the event.

CONCLUSION: Since it appears that CDSP is a significant independent predictor for ED, at both time points, males with diabetes should be assessed frequently for early warning signs and symptoms of sensory polyneuropathies. Further investigation of this area is warranted to determine if by preventing and/or delaying the polyneuropathies, ED can be delayed or even prevented.

5.2 INTRODUCTION

Neuropathies are common complications of type 1 diabetes (T1D) seen in approximately 50% of patients (Boulton et al., 2005). The most common neuropathies are the chronic sensorimotor distal symmetric polyneuropathies (DSP) and diabetic autonomic neuropathies (DAN). DSP is clinically evident with either an abnormal peripheral sensory exam and/or with decreased or absent deep tendon reflexes. However, when one of these signs is present along with an objective measure of decreased sensation it is considered to be Confirmed Distal Symetrical Polyneuropathy (CDSP) (Boulton et al., 2005; Orchard et al., 1990).

The presence of DAN significantly impacts morbidity and subsequently affects mortality. The markers for DAN include autonomic symptoms and measures of autonomic function such as Expiration/Inspiration Ratio (E/I ratio). Autonomic symptoms of DAN are 1) postural hypotension, 2) gastroparesis, 3) diabetic diarrhea, 4) colonic atony, 5) sudomotor abnormality, 6) hypoglycemic unawareness and 7) genitourinary autonomic neuropathy symptoms [including Erectile Dysfunction (ED) in males]. In addition, Symptomatic Autonomic Neuropathy (SAN) is defined as an average E/I Ratio of <1.1 and 2 or more of the other DAN autonomic symptoms.

One of the earliest markers of DAN in males with T1D is erectile dysfunction (ED). ED is defined as a persistent inability to attain and maintain an erection adequate enough to permit satisfactory sexual performance not due to any other problem and present for at least 30 days. ED is not viewed as a life threatening disorder; however, ED may be considered an important marker in the development and progression of cardiac and vascular disease (Kloner, 2008b). Males with diabetes have a 2-fold or greater increase in developing both ED and cardiac disease. ED shares many of the same risk factors with cardiac disease development and progression in males with T1D. These risk factors include increasing age, hypertension, hyperlipidemia, weight, depression, and certain medications. Given that ED is a significant marker for life-threatening disorders, understanding the sequence of its development vis-à-vis other complications is important. However, the pathological development of ED in relation to other neuropathies is not well defined.

Therefore, the purpose of this study was to identify the sequence to the development of ED in relation to other markers of neuropathy, i.e., E/I Ratio, Confirmed Distal Symmetrical Polyneuropathy (CDSP), and Symptomatic Autonomic Neuropathy (SAN). For

this analysis the hypothesis was that an E/I Ratio less than 1.1 would precede the development of ED.

5.3 RESEARCH DESIGN AND METHODS

All insulin dependent diabetes mellitus patients seen at Children's Hospital of Pittsburgh from January 1, 1950 to May 31, 1980 formed the sampling frame for inclusion in the Pittsburgh Epidemiology of Diabetes Complications Study (EDC). Participants had to meet the following criteria: 1) onset of insulin dependent diabetes mellitus at age 17 years or less; 2) insulin therapy prescribed at discharge; 3) an initial diagnosis, or being seen within one year following diagnosis at Children's Hospital of Pittsburgh; and 4) residence within 100 miles of Pittsburgh or 2.5 hours of driving distance from Pittsburgh. Recruitment and response rates for the EDC study have been detailed extensively in previous publications (Orchard et al., 1990). Six hundred and fifty-eight participants completed baseline examinations between 1986 and 1988.

Of the 658 participants enrolled at baseline (1986) for participation in the Pittsburgh Epidemiology of Diabetes Complications Study, 643 were Caucasian and 15 were African American. Thirteen of the African Americans were female participants and 2 were African American males. This sample was epidemiologically representative of the Allegheny County population and the incidence of T1D for that time frame.(Orchard et al., 1990; Wagener et al., 1982).

Males composed 51% (n=333) of the total sample. Age range for the males at baseline was from 8.5 years to 47.4 years. The duration of diabetes varied: 13% (n=44) had diabetes

for less than 10 years, 40% (n=136) had diabetes between 10 and 19 years, 35% (n=117) of the participants had diabetes between 20 and 29 years and, 11% (n=36) of the participants had diabetes for 30 years or more. Overall mean for duration of diabetes for all males was 19.5 years (sd ± 7.6 years). Ninety-nine percent of the males were Caucasian, 52% had never married, and, 36 % reported an income over $30,000 while 64% had incomes less than $30,000/year.

Because ED is only present in males who have reached an age of sexual maturity, an additional inclusion criterion for the ED study was age greater than or equal to an age of 18 years. Thirty-two of the 333 males were less than 18 years of age and baseline ED status was missing for three participants. However, as the 32 males reached 18 years of age they were entered into the risk set for the incidence analysis.

Participants received biennial examinations in the EDC center, by trained physician investigators, and were assessed for potential risk factors and diabetes complication development (Orchard et al., 1990). Follow-up examinations were conducted every two years and were similar to the baseline examination. Data were then collected biennially, for a period of 10 years (1986-1998). Cycle 1 through Cycle 6 exams took place over a 10 year period and included face-to-face clinic visits, physical assessments, laboratory testing and self report. Collection of data continued after the ten year follow-up with annual surveys , and a full examination at 18 years (Cycle 10:2006-2008) using the above methods. For this analysis, Cycles 2 through 6 and Cycle 10 were used.

5.3.1 Measures

5.3.1.1 Measure of Neuropathy

Physician investigators also inquired about diabetic autonomic neuropathy symptom while conducting the Diabetes Control and Complications Trial (DCCT) clinical neurological examination protocol that included questions relating to: 1) postural hypotension, 2) gastroparesis, 3) diabetic diarrhea, 4) colonic atony, 5) sudomotor abnormality, 6) hypoglycemic unawareness and 7) genitourinary autonomic neuropathy symptoms (i.e., ED in males).

5.3.1.2 Erectile Dysfunction (ED)

ED was to be present for at least 30 days prior to the examination. ED was a "yes or no" determination after genitourinary (GU) system review of 3 items by the examining physician. GU items included: 1) impotence, 2) retrograde ejaculation and, 3) lower urinary tract symptoms. Prevalent cases were those males reporting ED at baseline exam (1986-1988) while incident cases were those males who were negative for ED at baseline but developed ED during a follow-up cycle (1989-2007). The cycle in which the participant first reported ED following baseline examination was considered the incident cycle for ED. The incident ED cases were used for these analyses.

5.3.1.3 Expiration / Inspiration Ratio (E/I ratio)

Selected and trained research study staff completed the measurement procedure for the E/I ratio test. The E/I ratio, an autonomic nervous system function test, was measured with the participant in a supine position, limb EKG leads were attached and a lead II rhythm tracing recorded. The participant was then instructed to inhale deeply for 5 seconds followed by a forced expiration for 5 seconds and to continue this process of deep inspiration and forced expiration every 5 seconds for a total of 2 minutes. The participant was prompted by the examiner for determination of the 5 second intervals. The ECG was then marked to indicate an inspiration or expiration every 5 seconds during the recording for the total 2 minute testing time. Both the shortest R-R interval of each inspiration segment and the longest R-R interval of each expiration segment were measured in milliseconds. The E/I ratio was then calculated using the sum of six of the expiration (EXP) and inspiration (INP) R-R intervals using the following formula; sum of (R-R) EXP/ sum of (R-R) INP. Values < 1.1 were considered

5.3.1.4 Symptomatic Autonomic Neuropathy (SAN)

SAN was defined as having an average E/I Ratio of <1.1 and 2 or more of the other autonomic symptoms as determined by the examining physician using the DCCT neuropathy protocol previously described.

5.3.1.5 Confirmed Distal Symmetrical Polyneuropathy (CDSP)

CDSP was clinically evident DSP confirmed by physician's exam and a vibratory threshold of >2.39 for ages < 36 years, > 2.59 for ages 35-50 years, or > 2.89 for ages >50 years. . Data were coded as none (0), DSP (as defined above) and vibtoe negative DSP and vibtoe not available and, (1) DSP and confirmed with vibtoe.

5.3.1.6 Other Covariates

Hypertension was defined as a blood pressure greater than 140/90 mmHg or on anti-hypertensive medication. Blood pressure was measured per Hypertension Detection and Follow-up Protocol using a random zero sphygmomanometer. Mean of the second and third blood pressure readings were used and entered as a continuous variable for systolic and diastolic pressures separately.

Overt nephropathy (ON) was measured as an albumin excretion rate >200micrograms/min in multiple timed urine specimens, renal dialysis or a kidney transplant. Data for ON were coded none (0), or overt or renal failure (1).

Proliferative Retinopathy was determined from fundus photography and measured as none (0), or retinopathy and/or laser treatment for proliferative retinopathy (1).

Demographic Variables include continuous variables*: age (years), duration of diabetes (years), HbA1, systolic and diastolic blood pressure*, and *depression* (BDI); and categorical variables include*: marital status, level of education, income, and usage of ACE or lipid –lowering medications.*

5.3.2 Statistical Analysis

Analysis was performed using SAS (Version 9.1.3, SAS Institute Inc., Cary, NC). All data were verified after an extensive detailed exploratory analysis. Descriptive statistics were used to describe the sample. As mentioned, incident ED cases were used for these analyses. There was one multivariate outlier identified among the 54 incident cases. This data was verified and checked for accuracy. Since this outlier impacted the multivariate analysis, the decision was made to delete this case. SAN was not used for this analysis because one of the confirmatory autonomic symptoms was ED, which was considered a confounder and not used.

Cox proportional hazards modeling was used for the longitudinal data with time dependent covariates, controlling for duration. The cycle in which the ED event occurred was investigated for CDSP and E/I Ratio. Since the Cox proportional hazard model utilizes data points until the time of the event, a more robust model utilizing repeated measures to assess within and between differences was employed.

Also, lag variables (the variable for the preceding cycle) for CDSP and E/I Ratio were created to identify potential predictor variables in the cycle preceding the ED event. In developing the lag variables, in order to account for missing values, it was necessary to impute some of the missing values. In creating the lag variable for the E/I ratio there were 33 missing data points. In review of the E/I data, the imputed value was based on the Principle Investigator's expert opinion. The lag E/I variable for Cycle 2 incident cases was considered negative if the cycle 1 E/I variable was missing and the cycle 2 E/I value was negative.

5.4 RESULTS

Fifty-three males were identified as incident ED cases between 1988 and 2007. The 53 males that had ED were characterized by having a mean age of 40.61± 5.9 (range 26.7-60.8) years; a mean duration of diabetes 32.54 ± 5.88 (range 20.9-51-9) years; 69% (n=36) were married at the time of the reported ED; 74.5% (n=38) were college prepared, graduate or had professional degrees; 62% (n=32) had an annual income of $\geq$ $30,000; mean HbA1 of 10.68 ± 2.19 %, range 7.4-17; mean systolic and diastolic blood pressures 125. 29 ± 20.56 (range 88.0-191.0) mmHg and 75.57 ± 11.36 (range 49.0-108.0) mmHg, respectively; Sixty three percent (n=24) of the incident cases also had CDSP while 49 % were hypertensive. Average BECK score for depression was 9.34 ± 6.95 (range 0-32). Two thirds of the sample had diabetes duration for greater than 30 years while approximately one half of the sample was older than 40 years. Refer to Tables 5.1 and Table 5.2.

Table 5.1 Duration Distribution of the Incident Cases at Time of ED Event

Duration (Years)	n	% of total
20-25	8	14.8
25.1-30	10	18.5
30.1-35	18	33.3
35.1-40	14	25.9
40 +	4	7.5

Table 5.2 Characteristics of the 53 Incident Cases At Time of ED Event (1988-2007)

Age (m±sd) years	40 ± 5.96 Range: 26.27-60.90
Duration of Diabetes (m±sd) years	32.54 ± 5.94 Range: 20.9-51.90
Marital Stataus:	69.23 % n=36 (married at time of ED incident)
Level of Education	74.5% n=38(college/ graduate / professional)
Income	38% (n=19) annual income < $30,000
HbA1	10.68 (m±sd) 2.19 Range:7.4-17
Systolic Blood Pressure	125 (m±sd) 20.71 Range: 88-191
Diastolic Blood Pressure	76.10 (m±sd) 10.82 Range: 52-108
E/I Ratio	1.138 (m±sd) .123 Range: 1-1.545
CDSP	63.16% n=24
Retinopathy	73.08% n=38
Nephropathy	45.28% n=24
Hypertension	48.89% n=22
Taking Ace Medication	38.46% n=20
Taking Lipid Medication	4.55% n=2
Depression	9.34 (m±sd) 6.95 Range: 0-32
Age Categories (years)	<30 years = 2 (4%); 31-40 years = 21 (40%) 41-50 years = 27 (50%) 51-61 years = 3 (6%)

Univariate significant hazard ratios for the time of the reported ED event included: E/I Ratio, CDSP, and the controlled variables of hypertension, retinopathy, HbA1, and depression. When all variables were placed in the Cox regression model, only CDSP (3.70, 95% C.I: 1.99-6.72, $p<0.001$) was a significant independent predictor.

Preceding the ED event (the cycle before the incident cycle, with an average spacing of two years), univariate significant hazard ratios were CDSP, hypertension, proliferative retinopathy, nephropathy and HbA1. When all the lag variables were placed in a Cox model, only CDSP (3.14, 95% CI: 1.715-5.761, $p=.002$) again was the significant lagged independent predictor.

Taking into account variability, the significant variables from the repeated measures analysis at the time of the event included E/I ratio, time (cycle), duration of diabetes, HbA1, and depression. Whereby, the cycle before the reported incident ED, significant findings were for CDSP, time (cycle), duration of diabetes, and HbA1.

Table 5.3 Hazard Ratios of Variables at Time of Reported ED and at Cycle before the ED Event

Time of ED Event						Cycle Before ED Event				
Variable	Parameter estimate	se	p-value	Hazard Ratio	95%CI	Parameter estimate	se	p-value	Hazard Ratio	95%CI
E/I Ratio	-4.7899	1.27	.0002	.008	.001-.101	-1.16528	.88	.1836	.312	.056-1.75
CDSP	1.4537	0.29	<.001	4.28	2.41-7.6	1.2815	.30	<.001	3.60	2.01-6.47
Hypertension	0.8912	0.28	.0012	2.44	1.42-4.18	.7632	.28	.0062	2.15	1.24-3.77
Retinopathy	0.7817	0.31	.0120	2.19	1.18-4.02	.6885	.31	.0243	1.99	1.09-3.06
Nephropathy	0.7790	0.28	.0053	2.18	1.26-3.77	1.0708	.30	.0003	2.92	1.63-5.24
HbA1	0.1722	0.08	.0297	1.19	1.02-1.39	.2169	.08	.0075	1.24	1.06-1.46
Depression	0.0198	0.008	.0170	1.02	1.00-1.04	.0146	.02	.3154	1.02	.987-1.04

5.5 DISCUSSION

The sequence in the development of ED was examined in relation to other indicators of neuropathy namely E/I Ratio and CDSP, as well as other co-variates (hypertension, retinopathy, nephropathy, HbA1, and depression). The majority of men in this report were between the ages of 31-50 years with greater than 30 years duration of diabetes.

Current incident ED was univariately associated with E/I Ratio, CDSP, hypertension, retinopathy, nephropathy, HbA1 and depression, which all, except for E/I Ratio, have been previously reported in the literature (Fedele et al., 2001; Klein et al., 2005). Multivariate analysis resulted in only CDSP as being a significant independent predictor for incident ED.

This, too, has previously been reported in the literature (Klein et al., 2005). The repeated measures analysis at the time of the event included significant associations with E/I ratio, time (cycle), duration of diabetes, HbA1, and depression.

The cycle prior to the development of incident ED had lag variables that were univariately associated with incident ED were CDSP, hypertension, retinopathy, nephropathy and HbA1. The lag variables of E/I Ratio and depression were not associated with incident ED. In the multivariate analysis, CDSP, was the only significant independent predictor of incident ED in the preceding cycle. However, in the repeated measures analysis in the preceding cycle significant variables were CDSP, time (cycle), duration of diabetes, and HbA1. It appears then that CDSP may precede the development of ED. Unfortunately, we could not confirm that E/I Ratio also preceded the development of ED. To the best of our knowledge the sequence of these events has not been previously reported in the literature.

To our knowledge, lag variables have not been previously reported in the literature because ED has been used as a predictor of life-threatening events as opposed to being examined as the outcome variable.

There are several limitations, however, to this research and therefore the results of this analysis should be viewed with caution. The E/I ratio was missing for the analysis in the cycle preceding the event in 21 (39.6%) of the 53 cases. Imputed values were used for the missing values. These results were generated with imputed values and may not reflect the true clinical picture at the events times. This EDC longitudinal study is the gold standard of research. Following this EDC cohort provided the benefit of prospectively tracking the development of complications associated with diabetes over 21 years. However, problems following a cohort over this period of time include loss of patients to follow-up and mortality. It is difficult to

generalize these findings to the larger population of men with diabetes and ED due to the interval censoring.

It appears that CDSP is a significant independent predictor for ED 2 yrs before the occurrence of ED in males with diabetes. The E/I ratio was not a significant predictor for ED but based on the limitations of this study should not be discounted. Males with diabetes should be assessed frequently for early warnings of sensory polyneuropathies and early concurrent signs of ED. Further investigation of this area is warranted to determine if by preventing/or delaying the polyneuropathies, ED can be delayed/prevented as well, therby delaying/preventing some of the more life-threatening comorbidities.

6.0 OTHER RESULTS

6.1 GENERAL RESULTS

In addition to those demographic, biologic, lifestyle behavior, anti-hypertension use and psychosocial factors identified in Chapter 1, additional descriptives were generated to characterize the male cohort at baseline enrollment for the EDC. Please refer to Table 6.1.

Table 6.1 Characteristics for all Males at Baseline

	Total (N=333)
Age (m±sd) years	27.53±7.78 Range: 8.47-47.43
Duration of diabetes (m±sd) years	19.55±7.46 Range: 7.69-37.40
Age at onset of diabetes (m±sd) years	8.34 ± 4.17
HbA1c(m±sd) %	8.74 ±1.45 Range: 5.23-15.16
Systolic Blood Pressure (m±sd) mmHg	117.49±17.14 Range: 76-234
Diastolic Blood Pressure (m±sd) mmHg	75.52±11.20 Range: 44-118
BMI (m±sd)	23.59±3.1 Range: 13.87-33.12
Waist Hip Ratio (m±sd)	0.87±0.053 Range: 0.75-1.1
MARITAL STATUS (n,% total) **never married** **married** **separated** **divorced** **widowed** **not married, living with partner**	 175 (52.55) 131 (39.34) 2 (0.6) 18 (5.41) 0 7 (2.10)
LEVEL OF EDUCATION (n,% total) **SomeHS/HS graduate** **Some College** **Graduate**	 118 (39.46) 154 (51.51) 27 (9.03)
INCOME (% total) **<$5,000-$15,000** **$15,000-$30,000** **>$30,000**	 26.12 38.05 35.82
Smoking Ever(n,% total) **no** **yes** n=322	 190(59.01) 132(40.99)

Table 6.1 continued

Smoking Now(n.% total) **no** **yes** n=125	 50(40) 75(60)
Total alcohol (Average drinks /wk) N=192	6.17 ± 11.1 Range:0-53
High Density Lipoprotein (HDL)	48.61 ± 9.73
nonHDL Cholesterol	140.60 ± 44.56
Coronary Artery Disease (CAD) (n, % total) **no** **yes**	 305 (91.59) 28 (8.41)
+Autonomic Neuropathy (AN) (n, % total) **no** **yes** n=92	 60 (65.22) 32 (34.78)
+Symptomatic Autonomic Neuropathy (SAN) (n, % Total) **no** **yes** n=92	 83 (90.22) 9 (9.78)
Hypertensive (n,% total) **no** **yes**	 268 (80.72) 64 (19.28)
Nephropathy (n, % total) **no** **yes**	 238 (71.47) 95 (28.52)
Lower Extremity Arterial Disease (LEAD) (n, % total) **no** **yes**	 308(93.05) 23 (6.95)
Retinopathy (n, % total) **no** **yes**	219 (67.18) 107 (32.82)
Cerebral vascular Disease(CBVD)(n, % total) **no** **yes**	 331 (99.4) 1 (0.3)
Confirmed Distal Symmetrical Polyneuropathy (CDSP) **no** **yes**	 230 (69.27) 102 (30.73)
Distal Symmetrical Polyneuropathy (DSP) **no** **yes**	 227 (68.37) 105 (31.63)
Total Complications	1.18 ± 1.35 Range: 0-5

Table 6.1 continued

Ace Medication (n, % total) **no** **yes**	 307 (96.54) 11 (3.46)
Lipid Medication (n, % total) **no** **yes**	 317 (99.37) 2 (0.63)
Blood Pressure Medication (n,% total) **no** **yes**	 257 (90.49) 27 (9.51)
Quality Of Life (QOL) (m ± sd)	52.72 ± 12.19 Range: 33-129
Impact (m ± sd) (Domain within QOL instrument)	30.00 ± 6.75 Range: 19-53
Worry(m ± sd) (Domain within QOL instrument)	16.41± 6.42 Range:1-44
Satisfaction(m ± sd) (Domain within QOL instrument)	5.99 ± 1.96 Range: 3-11
Sex Question (m ± sd) (Question within Impact Domain/QOL Instrument)	1.72 ± 1.10 Range: 1-5
BECK Depression Inventory (BDI)**(m** ± sd)	6.2±6.20 Range:0-32

6.2 SPECIFIC AIMS

6.2.1 Secondary Specific Aim

Determine behavioral and cognitive risk factors, as represented by **self-management behavior, self-efficacy, perception of severity** and **knowledge** associated with the development of ED using EDC self- reported longitudinal data.

Question #1.: Does self-management behavior, self-efficacy, perceptions of severity and knowledge of diabetes predict ED?

Question #2: Is self-management a mediator between cognitive variables (self-efficacy, perceptions of severity and knowledge) and ED?

Complete data for the behavioral and cognitive risk factors were only found at baseline. Metabolic control (HbA1), self-management behaviors, knowledge, self-efficacy and beliefs were examined in 98 males without ED and 31 males with ED (matched for age and duration of diabetes). A significant, positive, difference (p=.04) was found between those with ED and those without ED for **knowledge** of diabetes. Borderline positive significance was found for **self-management** (p=.10) and **perception of severity** (p=.08) between those with ED and those without ED. However no significant difference was found between the two groups for **self-efficacy**. Non-significant correlations between ED and self-management behavior, self-efficacy, perception of severity and knowledge were found. See Tables 6.2 and 6.3 for presentation of findings.

Table 6.2 Biological, Behavioral and Cognitive Risk Factors in men with ED matched for Age and Duration to 98 males without ED at EDC baseline (1986-1988)

	ED(n=31)	No ED(n=98)	p-value
Age (years)	35.8 ±5.3	35.2 ±3.7	
Duration (years)	26.9 ±5.9	36.3 ±4.9	
HbA1	8.94 ±2.1	8.52 ±1.7	p>.05
Self-Management Behavior:			
1. Tested Weekly	58%	55%	p>.10
2. Based on Blood Glucose made changes to insulin	100%	98%	p=.10
Self-Efficacy: Can do something to control my diabetes and prevent/delay complications	85%	87%	p>.5
Perception of Severity:			
1. Perceive controlling glucose prevents/delays complications	81%	91%	p=.18
2. Perceive that by controlling glucose, complications are less severe	76%	90%	p=.08
Knowledge (good to excellent)	90%	73%	p=.04

Table 6.3 Association between ED and Self-management Behavior, Self-Efficacy, Perception of Severity, Knowledge and ED

	N=131	95% Confidence Limits	
Self-Management Behavior*			
• **Tested glucose**	.022	-.1730	.2175
• **Based on glucose changed insulin**	.069	-.0015	.1404
Self-Efficacy*	-.1163	-.3440	.1113
Perception of Severity*			
• **Perceive controlling glucose will prevent/delay complications**	-.1939	-.4308	.0430
• **Perceive controlling glucose will lessen severity of complications**	-.1990	-.4260	.0281
Knowledge*	.08499	-.0901	.2601

*Spearman Corrrelation p>0.05

7.0 CONCLUSIONS

7.1 SPECIFIC AIM #1

Determine both the age specific *prevalence* and *incidence* of *ED* obtained by self-report during physician interview.

The prevalence of ED in males with T1D enrolled at baseline in the Pittsburgh-EDC study was 10.4%. As age increased, the prevalence of ED also increased. The prevalence of ED rose from 2% in those 18-29 years of age to 42% in those 40-45 years of age. Sixty-one percent of the total ED cases (19/31) occurred in the males with ages between 30 and 39 years. With increasing duration of diabetes, the prevalence of ED also rose. Nineteen percent of the cases (n=6) occurred with a diabetes duration between 10 and 20 years, with the first case being reported after 10.7 years diabetes duration. Sixteen percent of the ED cases (n=5) occurred after 21-25 years of diabetes duration, 35% (n=11) occurred after 26-30 years duration while 29% (n=9) of the cases occurred after 31-37 years duration. This prevalence rate is somewhat lower than previously reported (20-60%) in the literature (Bacon et al., 2002; Bacon et al., 2003; http://www.diabetes.org/diabetes-statistics/prevalence.jsp, 2007; A Vinik et al., 2003).

Incidence was 17.78 % from 1989 to 2007 and reflects 53 new cases of ED. Person time at risk was 2034 person years, over 18 years, and, the incident rate per year was estimated at 2.6/100 /year. Ninety-five percent of the incident cases were between 30 and 49 years of

age. As seen with the prevalent cases, with increasing duration of diabetes, the incidence also rose. Our reported incidence rate was also lower than previously reported by Klein (Klein et al., 1996; Klein et al., 2005) at 25.6% and McCulloch (McCulloch et al., 1984) at 28%.

Different rates across studies may be due to varying definitions or measures used to assess ED. These differences can affect the sensitivity and specificity. For example, Klein et al (Klein et al., 1996) used participant self-report to ascertain cases. Males were asked to self-report ED by answering the following question "*Has diabetes caused impotence, that is an inability to achieve a normal erection?"*(Klein et al., 1996). Participants in this study might have over-reported impotence in that in replying yes to the question posed, they did not rule out other potential interactions between diabetes and/or other comorbidity treatment regiems. De Berardis et al (DeBerardis et al., 2005) used a self-report question , *"How often have you experienced problems in achieving and maintaining an erection during the past six months?* A Likert scale was presented for the patient to then make a selection from "never to more than once per week" and only those patients who selected more than once /week were then considered to have ED. A criterion then not only became a positive response to the occurrence of ED but a frequency in the occurrence as well. Several studies also have reported rates from specialty urology clinics and this higher representation may be the result of males with T1D presenting with more severe ED than those represented in a follow-up cohort such as the EDC, adding a severity factor to reporting ED as well.. Our study used the DCCT neurology criteria and the physician ruled out whether the ED was caused by diabetes. Some of the studies have used measures specific for ED such as the International Index of Erectile Function (Fedele, 1998) or structured interviews detailing presence, and severity of ED while others have used

more objective measures such as nocturnal penile tumescence and rigidity testing. Therefore the research methodology can not be ruled out as a factor affecting these rates.

There was no normative data to assess if the prevalence rates in males with T1D differ from the rates within the general population for the EDC. Additionally, studies completed within the early time frame of the EDC measured ED in males older than 40 and did not include the younger age groups. ED became a variable of interest in 2000 and was documented in a large national survey (NHANES) dataset; however, collection of this data did not coincide with the same time frame as our data. Therefore, no conclusion could be drawn as to whether the rates generated from our study were different.

7.2 SPECIFIC AIM #2

Determine baseline predictive risk factors for the development of ED.

From the multivariate analysis of the prevalent cases, only the biologic factors of duration of diabetes, CDSP and HDL were identified as independent predictors for ED while for the psychosocial model, the mean BDI symptomatology score was the significant independent predictor of ED identified.

The independent predictors for the 53 incident cases with ED were duration of diabetes, CDSP, nonHDL and weight. As found in the prevalence analysis, with the psychosocial variables for the incident cases, the mean BDI symptomatology score was the significant independent predictor of ED identified.

Both the prevalent and incident cases of ED had duration of diabetes, CDSP, lipid sub-fractions and BDI symptomatology as independent predictors of ED identified. In addition, the

additional independent predictor, weight, was identified for the incidence cases. Weight was not however identified in the EDC prevalence analysis.

Several studies have confirmed the association of duration of diabetes and ED (Klein, 1996; Bacon,2006; Kloner RA,2008). The first case for the prevalent ED cases was after 10.7 years whereas the first case for the incident cases was 20.4 years. This confers with similar findings previously reported (Burnett, 2006; Fedele, 1998; Fedele et al., 2001; Klein et al., 2005) . The most probable hypothesis for the increased association between ED and diabetes duration may in part be due to the effects of sustained and variable levels of glucose on the cavernosal tissue. The accumulation of advanced glycolsalated end products (AGEs), the consequence of long term hyperglycemia, most probably mediate many of the complications of diabetes to include cardiovascular disease, neuropathy and nephropathy. The role of the accumulating AGEs in the pathology of ED is its association with the impairment of the endothelial dependent reduction in endothelial nitric oxide synthatase expression (A. Seftel et al., 1997) Effects of diabetes on the protein kinase C-beta expression/activation in cavernosal smooth muscle can lead to exaggerated contractile penile responses and thereby impair erectile function (Gantz & Seftel, 2002). Diabetes is thought to be an age accelerating disease due to the effects of the diabetes disease process on endothelial function at the cellular level with a resultant acceleration in atherosclerosis development. The longer someone has diabetes, the faster the effects of this accelerating aging effect are seen, especially in the absence of tight metabolic control. For those with diabetes this may be the reason ED is seen 10 to 15 years earlier than in the general population.

HDL cholesterol, in the prevalent cases, and nonHDL cholesterol for the incident cases were significant predictors. Although ED has causal neuopathic pathways , there are also most probably vascular pathologies associated with its development (A. D. Seftel et al., 2004) as well. Higher levels of non-HDL has been associated with endothelial dysfunction and vascular aging (Thomas et al., 2008). Hypercholesterolemia has been associated with impairment of endoththieum dependent relaxation in smooth muscle cells of the corpus cavernosum (DeBerardis et al., 2007). Impaired endothelial dysfunction results from the modification of the nonHDL cholesterol by glycation, as in those with diabetes, oxidation or incorporation into immune complexes which contribute to vascular smooth muscle and endothelial dysfunction (Ross, 1999). In the prevalent cases HDL cholesterol was a predictor and was noted to be significantly lower than in the males without ED. This association may be the resultant effect from vascular stiffness and atherosclerosis development. These abnormal lipid levels may be the common pathway for ED as well as the other macrovascular complications frequently seen in diabetes. The association of lipid abnormalities with ED have been previously reported in the literature (Fedele et al., 2001; Klein et al., 2005).

In both the prevalent and incident cases, confirmed distal symmetrical polyneuropathy was found to be a significant predictor of ED. This has been previously reported (Fedele, 1998; Klein et al., 2005; Saigal et al., 2006). Klein (Klein et al., 1996) found a relationship between lower extremity pain on ambulation and incident erectile dysfunction in a 1996 prevalence study from Southern Wisconsin in a group of youth-onset diabetes males. It is hypothesized that the effect of repeated hyperglycemia causes endoneuronal microangipathic change within all sensory nerves which then proceeds to the loss of nerve fibers, especially in the lower extremities and trunk (Yagihashi, 2007)..

Further, this then causes a decrease in the small skin fibers affecting skin sensitivity to stimuli. All of the above therefore contribute to the development of ED in males with T1D.

Weight was identified as an independent predictor for the incidence cases but not in the prevelant cases. Weight has been previously reported in the literature as well for its association to ED development, diabetes and cardiovascular disease. The association with the effect of weight may be organic but the effect may also have a psychogenic origin. Increased weight affects body-image which may affect self-esteem. This may then lead to a decline in quality of life and expression of depressive symptomatology which has been linked with ED (Shiri et al., 220).

Finally, the psychosocial predictor variable, BDI symptomatology score, found in this analysis for both prevalence and incidence has previously been reported as well. From this study, we concluded that the BDI score was an independent predictor of ED in both the prevalent and incident cohort. Although this score for both those males with ED and without ED was not in the moderate or severe depressive symptomatology range, there was a statistically significant difference between the two groups. It is unknown however, if ED was caused by the depressive symptomatology or whether the depressive symptomatology (higher BDI score) was concurrently present as a result of another disease process. The effect of this expression of depressive symptomatology can result from organic causes, mainly an inhibition of the parasympathetic nervous system which affects the blood flow to the penis causing inhibition of penile smooth muscle relaxation (Shiri et al., 220). The effect on erectile function may be psychological as well. Psychosocial explanations have been given as reactive depression effect, i.e., the male's partner negatively reacts to the depression as a result of the males loss of sexual functioning (Shiri et al., 220).

7.3 SECIFIC AIM #3

Determine the sequen ce of the d evelopment of ED in relation to other markers of neuropathy, i.e., Autonomic Neu ropathy *(AN)(* E/I ratio <1.1), Confirmed Distal Symmetrical Polyneuropathy *(CDSP),* and Symptomatic Autonomic Neuropathy *(SAN)* *(*excluding ED) using longitudinal data.

The sequence in the development of ED was examined in relation to other indicators of neuropathy namely E/I Ratio and CDSP as well as hypertension, retinopathy, nephropathy, HbA1, and BDI score. Multivariate analysis resulted in only CDSP as being a significant independent predictor for incident ED. This, too, has previously been reported in the literature (Klein et al., 2005) and has been previously discussed for Specific Aim #2. The repeated measures analysis at the time of the event included significant associations with E/I ratio, time (cycle), duration of diabetes, HbA1, and BDI score.

Two years prior to the development of incident ED the lag variables that were univariately associated with incident ED were CDSP, hypertension, retinopathy, nephropathy and HbA1. The lag variables of E/I Ratio and BDI score were not associated with incident ED. In the multivariate analysis, CDSP, again, was the only significant independent predictor of incident ED in the preceding cycle. However, in the repeated measures analysis in the preceding cycle significant variables were CDSP, time (cycle), duration of diabetes, and HbA1.

To our knowledge, lag variables have not been previously reported in the literature because ED has been used as a predictor of life-threatening events as opposed to being examined as the outcome variable.

It appears then that CDSP may precede the development of ED. We could not confirm that E/I Ratio also preceded the development of ED. For CDSP to be positive, in addition to the clinically evaluated physical signs, an age-specific vibratron score was also necessary to delineate the neuropathy. This may be a very sensitive marker for neuropathy. The E/I ratio may not have been as sensitive in determining sub-clinical neuropathy in this cohort, and hence, non-confirmation as a marker for ED. Although the exact pathway was not determined, the association with CDSP preceding the development of ED may share a common pathway with metabolic control, hypertension and duration of diabetes. To the best of our knowledge the sequence of these events has not been previously reported in the literature.

7.4 SECONDARY SPECIFIC AIM

Determine *behavioral and cognitive risk factors*, as represented by self-management behavior, self-efficacy, perception of severity and knowledge associated with the development of ED using EDC self- reported longitudinal data.

Complete data for the behavioral and cognitive risk factors were only found at baseline. Metabolic control (HbA1), self-management behaviors, knowledge, self-efficacy and beliefs were examined in 98 males without ED and 31 males with ED (matched for age and duration of diabetes). A significant positive association (p=.04) was found between those with ED and those without ED for knowledge of diabetes. Borderline significance was found for self-

management (p=.10) and perception of severity (p=.08) between those with ED and those without ED. However no significant difference was found between the two groups for self-efficacy. Non-significant correlations between ED and self-management behavior, self-efficacy, perception of severity and knowledge were found. This was a retrospective analysis of self-management behaviors, knowledge, self-efficacy and perceived susceptibility to diabetes complications. The Social Cognitive umbrella of theories was chosen as the conceptual framework to fit the data that was present at baseline, and hence was not theory generating in the EDC's original design. Specific questions were chosen from the baseline Questionnaires to fit the behaviors, attitudes, knowledge and awareness. Although the self-management data was present longitudinally, some of the baseline questions for the remaining were deleted over time of the study.

7.5 OVERALL SUMMARY

In conclusion, results of this study were confirmatory of what has been previously reported in the literature for the demographic, biologic, behavioral lifestyle and psychosocial risk factors for predicting prevalent and incident ED. Although both the prevalence and incidence rates were lower than previously reported, this study's uniqueness was in the physician's assessment of ED based on the DCCT neuropathy examination protocol. As a result of this physician assessment then, this study may have therefore provided a more accurate description in males with T1D and ED. CDSP was identified as significant factor proceeding in time to ED development. This to our knowledge has not been previously reported and further investigation is warranted. Confirmation that males with diabetes and ED engaged in self-

management behaviors for diabetes control occurred. However we were unable to describe the longitudinal relationship of these behaviors to self-efficacy, level of diabetes knowledge, and, the male perception of the severity as they related to ED development over time. These variables of interest were retrospectively designed for this analysis from baseline questionnaire data, and other than the self-management behavior variable were not maintained longitudinally. . Therefore no conclusion could be drawn concerning the variables of self-efficacy, knowledge of diabetes, and, perceived susceptibility of complications.. It is imperative to have a better understanding though of this to affectively change, if necessary adherence to diabetes treatment regimes.

7.6 LIMITATIONS

There are several limitations to this study, the first of which lies in the methodology. This study started in 1986, fourteen years before ED became an interest in the general population and before validated questionnaires for ED, ie, the International Index for Erectile Function, and the DMS-QOL were available. Although ED was based on the DCCT clinical autonomic neuropathy review, the decision was made by the physician examiner. Since this was a secondary analysis, there were no quality control measures to assess inter-rater reliability in place for ED, and, therefore, it is not known if ED is under/over reported in this EDC cohort. Previous literature cites the gender of the examiner to affect reported and discussion of ED in males with diabetes. Males were more likely to report ED to male examiners, but with female physician examiners in order for a discussion of ED to ensue, the female physician had to have posed the question for dialogue to occur. In the EDC cohort, the males were three times more

likely to report ED symptomatology to male examiners then their female physician counterparts. This however, after review of the data, was not statistically significant but warrants mentioning.

A second limitation is that this cohort upon the start of the study was all ready an aged cohort for youth-onset diabetes. The mean age of the males was 27.53 $\pm$ 7.78 years (range: 8.47-47.43) and mean duration of diabetes was 19.55 $\pm$ 7.46 (range: 7.69-37.40) years. Although the low enrollment of African Americans was reflective of the population in Allegheny County utilizing services at Children' Hospital of Pittsburgh and of the low incidence of T1D seen in the African American population at the time of the study's inception these results may not be generalizable to other racial groups with diabetes. This population was almost all Caucasian, so it is unknown if these findings hold true for other racial populations.

This EDC longitudinal study is the gold standard of research. Following this EDC cohort provided the benefit of prospectively tracking the development of complications associated with diabetes over 18 years of follow-up. However, problems following a cohort over this period of time include loss of patients to follow-up and mortality. Therefore, it may be difficult to generalize these findings to the larger population of men with diabetes and ED due to this interval censoring. The critical factor here lies in the assumption that the reason a male was censored was independent of or unrelated to the development of ED.

This study provided an exploratory descriptive analysis of ED in this cohort of males with T1D. However, due to the small sample size, all arithmetic multiplicative interactions between variables, i.e. age at diagnosis of diabetes and ED, were not independently assessed as main effects..

7.7 IMPLICATION FOR NURSING AND PUBLIC HEALTH

As previously stated, diabetes is one of the major chronic diseases seen today that imparts significant public health and economic burden on society. Complications from diabetes are costly and result in excess morbidity and mortality. Understanding the long term complications of diabetes, the intra-relationships among these complications and the risk factors is important. It is with this understanding that complication rates will decrease and an improvement in the quality of life of those affected by diabetes will occur. Although ED is not considered to be a life threatening complication, the development of ED is associated with other more life threatening concurrent complications so there is necessity in investigating this further.

Larger prospective studies should evaluate the effect of early treatment and intervention to prevent sensory polyneuropathy, control of blood lipids, and depression using standardized objective measures specific to ED. Evaluations of the present sub-clinical neuropathy diagnostic procedures, i.e. E/I ratios, should reflect the most sensitive measure to diagnosis sub-clinical autonomic neuropathy earlier. As with the CDSP measures, larger trials should evaluate the effect of age, weight, comorbid conditions and ethnicity on these measures. When designing studies of ED in males with T1D, it is necessary to have the participants of those studies report the ED event when it actually occurs, thereby assuring that the risk factors can be assessed at the time of development. Having the participant recall the time of the event results in under-reporting due to recall bias, presents mathematical issues with interval censoring and may not actually reflect the metabolic or disease state at the time of the event occurrence. Quality of life should be evaluated using a sexual function specific evaluation tool. Since glycemic control has been shown previously to delay ED from occurring, the self-management

behaviors, self-efficacy, knowledge of diabetes and ED, and perceived susceptibility for risk of ED should be explored. It is imperative to have a better understanding of the impact of these behaviors, attitudes and beliefs surrounding ED and other diabetes complications if adherence to the diabetes treatment regime is to be affected. Since there have been previous reports within the literature that males are reluctant to seek help for ED, qualitative studies are needed to explore this further also. These qualitative studies should identify the recurring themes to help understand these behaviors and attitudes of males with respect to their T1D and ED. Also, these qualitative studies need to be in place in the adolescent populations as well to explore their knowledge of, beliefs and attitudes toward long term reproductive issues of males with T1D. After determination of the above, diabetes education programs can be developed, evaluated and implemented specific to reproductive health issues for males with diabetes. Diabetes educators should encourage narrative about reproductive issues in males and in teens this information should be reviewed as part of their diabetes education program. Since it appears that CDSP is a significant independent predictor for ED, generated 2 yrs before the event, males with diabetes should be assessed frequently for early warnings of sensory polyneuropathies. Further investigation of this area is warranted to determine if by preventing/or delaying the polyneuropathy, ED can be prevented or delayed as well.

It should not be overlooked, however, that sex plays a very important role in the males' life with diabetes, and raising awareness of risk factors of ED and diabetes adds to the significance of this study. It is equally important to note that our study found a difference in self-report of ED by gender of the physician. As nurses we need to therefore be sensitive to this issue and develop strategies in interviewing males with diabetes as to these matters.

APPENDIX A: SUMMARY OF ED STUDIES

NAME OF STUDY	YEAR OF STUDY	N Ages	TYPE OF STUDY	ED QUESTION	IDENTIFIED RISK FACTORS
MASSACHUSETTS MALE AGING STUDY (MMAS)	1987-1989	1290 40-70	CROSS-SECTION	SEXUAL ACTIVITY SURVEY-SELF-REPORT	DIABETES,HEART DISEASE, ANGER, DEPRESSION, HYPERTENSION, HDL, CIGARETTE SMOKING, EDUCATION, OCCUPATION
NATIONAL HEALTH LIFE SURVEY	1992	1410 18-59	CROSS-SECTION	SELF-REPORT; "INABILITY TO ACHIEVE AN ERECTION	AGE, STRESS, SOCIOECONOMIC STATUS, RACE
HEALTH PROFESSIONAL FOLLOW-UP SURVEY	2000	43,235 53-90	CROSS-SECTION	SELF-REPORT-ED ON SURVEY	<PHYSICAL ACTIVITY > 20 HRS OF TV VIEWING/WEEK, SMOKING, DIABETES, STROKE, CANCER, HYPERTENSION
MANAGED CARE RECORD REVIEW	1995-2001	285,436 18-86	COHORT	ED DIAGNOSIS IN MEDICAL RECORD SELF-REPORT	HYPERTENSION LIPIDEMIA, DIABETES, DEPRESSION

MULTINATIONAL MEN'S ATTITUDE TO LIFE EVENTS AND SEXUALITY	2000	28,691 20-75	MULTIPLENATIONS CROSS-SECTION	SELF-REPORT SURVEY	HYPERTENSION, LUTS, POOR HEALTH
NATIONAL HEALTH AND NUTRITIONAL EXAMINATION SURVEY (NHANES)	2001-2002	10,000 >20	CROSS-SECTION	SELF-REPORT UNABLE TO KEEP AN ERECTION	DIABETES, HYPERTENSION, OBESITY,>IN HISPANIC MEN
EDINBURGH DIABETIC OUT-PATIENT DEPARTMENT STUDY Type 1 and type2 diabetes	1980	563 20-59	CROSS-SECTION	INTERVIEW-SELF-REPORT	RETINOPATHY AUTONOMIC NEUROPATHY, POOR DIABETES CONTROL, AGE ISCHAEMIC HEART DISEASE
KLEIN ET AL WISCONSIN COHORT TYPE 1 DAIBETES	1996	1210 >21	CROSS-SECTION	"HAS DIABETES CAUSED IMPOTENECE, AN INABILITY TO HAVE AN ERECTION?"	PERIPHERAL NEUROPATHY, CAD, >BMI, >DURATION OF DIABETES, , ON B/P MEDS, SEVERE RETINOPATHY

KLEIN ET AL Wisconsin T1D	2000	365 21-64	AFTER 10 YEARS ABOVE STUDY	SELF-REPORT OVER 10 YR PERIOD	HYPERTENSION, AGE, CHOL, SMOKING, LOWER EXTREMETRY PAIN ON WALKING
FEDELE ITALIAN STUDY T1D & T2D	1998	9868 20-69	CROSS-SECTION	ARE YOU SATISIFED WITH YOUR SEXUAL PERFORMACE	POOR CONTROL OF DIABETES, ARTERIAL, RENAL, RETINAL DISEASE, , NEUROPATHY, SMOKING BMI
SIU HONG KONG STUDY T1D &T2D	1999	486 21-80	CROSS SECTION	SELF-REPORT SURVEY	AGE, DURATION, RETINOPATHY, ALBUMINURIA, SENSORY POLY-NEUROPATHY, HIGH LEVEL OF EDUCATION
ENZLIN BELGIUM STUDY T1D	2003	240 >18	CROSS SECTIO	UDVALG FOR KLINISKE UNDERSOE-GELSER SEXUAL SURVEY	AGE, BMI, DURATION OF DIABETES, DIABETES COMPLICATIONS

DEBERARDIS STUDY T2D	2003	670	EVERY 2 YEARS FOR FOLLOW -UP	HOW OFTEN DO YOU HAVE PROBLEMS TO MAINTAIN AN ERECTION	AGE, INSULIN HBA1, CHOL, SEVERITY OF DEPRESSIVE SYMPTOMS
BORTOLOTTI ITALIAN STUDY	1996	9670 20-70	CROSS SECTION	SELF-REPORT ABILITY TO MAINTAIN ERECTION	SMOKING
DCCT/EDIC UROEDIC STUDY T1D unpublished results	2003	571	COHORT	INTERNATIONAL INDEX OF ERECTILE FUNCTION (IIEF)"OVER THE PAST 4 WEEKS, HOW WOULD YOU RATE YOUR CONFIDENCE TO KEEP AN ERECTION?"	PERIPHERAL NEUROPATHY, AGE, HBA1 AT DCCT BASELINE, LUTS,
DCCT/EDIC UROEDIC STUDY T1D	2003	591	COHORT	OIIEF ORGASMIC DYSFUNCTION ,DECREASED LIBIDO, QUALITY OF LIFE	ED HAS >IMPACT ON QOL, AND >BOTHER

APPENDIX B: IRB

University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Ground Level
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)

MEMORANDUM

TO: Trevor Orchard, MD

FROM: Robert Sweet, MD, Vice Chair

DATE: February 12, 2008

SUBJECT: IRB #980707: The Epidemiology of Diabetes Complications: Phase II

Your renewal was reviewed by the Institutional Review Board and approved at the Full Board Meeting (Committee A) that met on Tuesday, February 5, 2008.

Please include the following information in the upper right-hand corner of all pages of the consent form:

Approval Date: February 5, 2008
Renewal Date: February 4, 2009
University of Pittsburgh
Institutional Review Board
IRB #980707

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. The IRB Reference Manual (Chapter 3, Section 3.3) describes the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1504.

The protocol and consent forms, along with a brief progress report must be resubmitted at least one month prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

If this research study is subject to FDA regulation, please forward to the IRB all correspondence from the FDA regarding the conduct of this study.

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

RS:dj

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