FACTORS ASSOCIATED WITH SURVIVAL FOR A COHORT OF
CLINICALLY CONFIRMED DIABETES CASES IN NOVA SCOTIA

by

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DEDICATION PAGE

This thesis is dedicated to my late father, Amos Lewis – I wish he could be here to celebrate this great accomplishment.

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ABSTRACT

Diabetes Care Program of Nova Scotia (DCPNS) Registry data were used to examine factors associated with survival for clinically confirmed diabetes mellitus (DM) cases. Type 1 (N=2,043) and type 2 (N=47,974) cases were followed from first Diabetes Centre visit until death/study end. Kaplan Meier curves and Cox proportional hazard models were used to explore differences in survival by sex, district health authority of care, and comorbidity status (hypertension and/or dyslipidemia). Median lifespan for type 1 cases was 12 years shorter than for type 2 cases. Hazard rate ratios for those with dyslipidemia, hypertension, or both compared to those with neither comorbidity were 1.63, 2.57, and 7.52 for type 1 cases and 0.95, 1.15, and 1.00 for type 2 cases. Disease progression and the relationship between comorbidity status and survival differed markedly for the type 1 and type 2 DM populations underscoring the need to examine these populations separately.

LIST OF ABBREVIATIONS

A1C   Glycated haemoglobin

CDA   Canadian Diabetes Association

CPG   Clinical practice guidelines

DC   Diabetes Centre

DCPNS   Diabetes Care Program of Nova Scotia

DHA   District Health Authority

DM   Diabetes mellitus

FPG   Fasting plasma glucose

GDM   Gestational diabetes mellitus

HRR   Hazard rate ratio

ICD-9-CM   International Statistical Classification of Diseases and Health Related
             Problems, 9th Revision, Clinical Modification

IFG   Impaired fasting glucose

IGT   Impaired glucose tolerance

IWK   Isaak Walton Killiam

LDL-C   Low density lipoprotein cholesterol

MSI   Medical Services Insurance

NDSS   National Diabetes Surveillance System

NS   Nova Scotia

ODD   Ontario Diabetes Database

OGTT   Oral glucose tolerance test

PAD   Peripheral arterial disease

PG   Plasma glucose

PHAC   Public Health Agency of Canada

RCMP   Royal Canadian Mounted Police

2hPG   Two-hour plasma glucose

ACKNOWLEDGEMENTS

CHAPTER 1: INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder marked by abnormally high blood glucose levels. Although this disease is associated with an array of micro- and macro-vascular complications, the exact mechanisms by which these complications arise are not well understood.[1,2] Individuals with DM are also at increased risk for premature death[3-4]; however, our understanding of survival (i.e., the trajectory from birth, to DM diagnosis, to the development of comorbidities, and eventually to death) is not well understood due to limitations with existing data sources. A key limitation underlying much of the Canadian DM literature is the ascertainment of true DM cases with a known date of diagnosis and DM type. The burden of DM also varies across jurisdictions[3,5,6] so information from one country, province, or region may not generalise to another. As such, it is important to examine DM and associated factors at the local level.

Nova Scotia is unique in Canada in that the Diabetes Care Program of Nova Scotia (DCPNS) maintains a population-based, longitudinal Registry (DCPNS Registry) of over 75,000 clinically confirmed cases of DM/prediabetes referred to the provinces 39 Diabetes Centres (DCs). The richness of these data permits the identification of exact date of DM diagnosis, DM type, comorbidities present at time of first DC visit, and date of death. Together, these factors provided an unprecedented opportunity to explore the factors associated with survival (i.e., from birth to death) for a large population-based cohort of clinically confirmed cases of DM.

Diabetes Mellitus

Definition and Diagnostic Criteria

Diabetes mellitus is a metabolic disorder marked by abnormally high blood glucose levels. This disease has been recognized since ancient times; yet, our understanding of its nature continues to evolve. In Canada, diagnostic criteria for DM are published in the Canadian Diabetes Association (CDA) Clinical Practice Guidelines (CPGs) for the Prevention and Management of Diabetes in Canada. Four sets of CPGs have been

released over the last 15 years (see Appendix A); the current criteria are presented in Table 1.1.

A diagnosis of DM can be made on the basis of a casual plasma glucose (PG), a fasting plasma glucose (FPG), or a 2-hour plasma glucose (2hPG) resulting from an oral glucose tolerance test (OGTT).[7] In the absence of unequivocal DM symptoms (e.g., polyuria, polysypsia, etc.) and acute metabolic decompensation, a confirmatory blood test (FPG, casual PG, or OGTT) must be performed on a different day before assigning a diagnosis of DM.[7]

Table 1.1: **Diagnostic criteria for diabetes from the Canadian Diabetes Association Clinical Practice Guidelines[7]**

Diagnosis	Casual PG (mmol/L)		FPG (mmol/L)		2hr PG after 75g OGTT (mmol/L)
Diabetes	≥ 11.1	or	≥ 7.0	or	≥ 11.1
Isolated IFG	–		6.1-6.9	and	< 7.8
Isolated IGT	–		< 6.1	and	7.8-11.0
IFG & IGT	–		6.1-6.9	and	7.8-11.0

FPG = Fasting plasma glucose (i.e., no food or beverage for at least 8 hours)
IFG = Impaired fasting glucose
IGT = Impaired glucose tolerance
OGTT = Oral glucose tolerance test
PG = Plasma glucose

Prior to 1998, the diagnostic threshold for a FPG was 7.8 mmol/L.[8] In 1998, the threshold was reduced to 7.0 mmol/L, a value that correlated more strongly with a 2hPG of 11.1 mmol/L and better predicted the development of microvascular complications.[9]

The CDA CPGs recognizes four aetiological categories of DM: type 1, type 2, gestational diabetes (GDM), and other specific types.[7]

- A diagnosis of **type 1 DM** is assigned when the pancreas produces little or no insulin due to the destruction of the insulin-producing beta cells. Previous terminology for type 1 DM includes juvenile DM and insulin-dependent DM.
- A diagnosis of **type 2 DM** is assigned when the pancreas either produces an insufficient quantity of insulin and/or the body is resistant to the insulin it

produces. Previous terminology for type 2 DM includes adult-onset DM and non-insulin dependent DM.

- A diagnosis of **GDM** is assigned when the onset of DM first occurs during pregnancy. Unlike type 1 and type 2 DM, GDM is transitory, usually subsiding after parturition. If high blood glucose values persist after parturition, GDM will be reclassified as one of the other types (e.g., type 1, type 2, other specific types).
- A diagnosis of **other specific types of DM** is assigned for a wide range of relatively rare metabolic conditions, many of which are caused by genetic mutations, drug use, or other disease processes (e.g., cystic fibrosis, congenital rubella, Cushing syndrome, etc).

In 2003, the CDA formally introduced the term prediabetes as a label for three different conditions characterized by glucose levels that are elevated but not yet in the range of DM: isolated impaired fasting glucose (IFG), isolated impaired glucose tolerance (IGT), and IFG & IGT combined.[10] Individuals with prediabetes, compared to those without the condition, are at increased risk for developing DM and cardiovascular disease.[7,10]

A knowledge of DM type is very important to understanding the trajectory of the disease. Type 1 DM typically, though not always, develops during childhood/adolescence and presents as an acute health crisis that can quickly result in death if left untreated. Type 2 DM typically develops much later in life and may go undiagnosed for many years.[11,12] As a result, between 20% and 50% of type 2 DM cases have micro and/or macrovascular complications present at time of diagnosis.[7]

Prevalence and Incidence

In 2000, the estimated global prevalence of DM among adults ($\geq$20 years) was 4.6%.[5] However, this figure varies widely by country, from less than 1% in several African countries (e.g., Angola, Guinea) to 8.8% in Canada, and over 20% in the Arab Emirates and Nauru.[5] Because of these variations in prevalence estimates, epidemiological information from one jurisdiction cannot be generalised to another. For this reason, only Canadian data will be presented from this point forward.

In 2001, the National Diabetes Surveillance System (NDSS) was established to address a critical gap in information about the burden of DM in Canada by using routinely collected administrative health records (physician billings and hospital discharge abstracts) available in all provinces and territories to estimate the prevalence and incidence of DM.[13] Using the NDSS methodology, DM cases are identified on the basis of one hospitalization or two physicians' claims within a 730-day period (2 years) with a DM code.[13]

The NDSS has shown that even within Canada, there is tremendous variation in the prevalence and incidence of DM. In fiscal year 2005/06, the age-standardized prevalence of DM (type 1 and type 2, combined) among the population aged 1 year and older ranged from a low of 4.5% in Alberta and Québec to a high of 5.7% in New Brunswick and Nova Scotia.[6] In Nova Scotia, the age-standardized prevalence of DM (type 1 and type 2, combined) among the adult population (≥ 20 years) for fiscal year 2008/09 was 8.1% overall.[3] At the district health authority (DHA) level, this value ranged from a low of 7.7% in Capital, Cumberland County, and Pictou County DHAs to a high of 9.4% in Cape Breton DHA.[3] The age-standardized incidence for this population was 7.6 per 1,000 population for the province as a whole, with a low of 6.1 in Cumberland County DHA and a high of 8.6 in South West Nova DHA.[3]

Although the NDSS methodology is useful for generating nationally comparable figures across relatively short periods of time; it has a number of limitations due to its reliance on administrative data. Diabetes cases identified through administrative health records are not necessarily clinically confirmed cases. The inaugural report of the NDSS noted that false positive cases accumulate over time resulting in an overestimate of DM prevalence.[13] Without an exit rule to help eliminate false positive cases, this problem gets more serious with each additional year of data used. Another key weakness of using administrative health records for DM surveillance is that the true date of diagnosis is unknown. The NDSS uses a proxy measure – the date that an individual first met the case definition – that can be problematic, especially for mobile populations (youth/young adults, Armed Forces, RCMP, etc). Because NDSS cases are not tracked from province to province, recent migrants to a province will appear to be incident cases when in fact they could have had DM for many years. In addition, the NDSS methodology cannot

distinguish DM type. Finally, the majority of NDSS DM cases are identified through physician billings records. In Nova Scotia, these records are coded using the International Statistical Classification of Diseases and Health Related Problems, 9th Revision, Clinical Modification (ICD-9-CM), which lacks separate codes for DM type at the three digit level. This problem was corrected in the 10th revision.

Disease Progression

Diabetes is associated with a wide array of complications that can be divided into two broad categories, microvascular and macrovascular, based on the underlying pathophysiology. All small blood vessels sustain damage as a result of DM; however, the vessels of the retina, glomeruli, and certain nerves are particularly susceptible giving rise to diabetic retinopathy, nephropathy, and neuropathy.[1] The exact mechanisms that give rise to these microvascular complications are not well understood and vary depending on the vessels involved.[1,2]

Macrovascular complications associated with DM include heart disease, central nervous system disorders, cerebrovascular events, and peripheral vascular disease.[1,2] Although these conditions are not unique to DM, they are more prevalent among DM cases and occur at younger ages.[7] Together, they account for over 75% of deaths among DM cases.[7] Again, the underlying pathophysiology of these complications is not well understood; however, excessive and accelerated atherosclerosis, prolonged periods of hyperglycaemia, and glycoprotein formation are believed to play a role.[1,2]

There is little debate about the fact that DM is associated with increased morbidity and premature mortality. However, our understanding of the trajectory of DM from onset, to the development of comorbidities, and eventually to death is not well understood due to limitations with existing data sources. Key limitations of most studies are ascertainment of true DM cases, a true date of diagnosis, and DM type.

A 25-year prospective cohort study of 4,376 Quebec men showed that the age-adjusted risk for cardiovascular-related mortality and all-cause mortality was 2.7 and 1.8 times higher respectively for those with type 2 DM versus those without DM.[14] For

approximately 66% of cases, a diagnosis of incident DM was assigned based on subjects' self-report; for the other 33% of cases, the diagnosis appeared to be based on a FPG ≥7/0 mmol/L.[14] Using this method of assigning date of diagnosis can result in both bias and incomplete case ascertainment. Self-reported date of diagnosis is subject to the telescoping effect – a tendency to recall that a recent diagnosis occurred further back in time or that a long-standing diagnosis occurred more recently. Assigning date of diagnosis based on FPG will systematically exclude cases with normal FPG but with a casual or 2hPG over 11.1 mmol/L. This exclusion is of particular concern as impaired post-prandial glucose (i.e., as measured by 2hPG) is more strongly associated with increased cardiovascular risk than impaired fasting glucose.[7] Using a single FPG glucose to rule in cases will also result in some misclassification of non-cases as a true diagnosis of DM[7] requires a second confirmatory test in the absence of unequivocal DM symptoms and acute metabolic decompensation.

When comparing a sample of over 610,000 adults 35 years of age and older newly identified as having DM through the Ontario Diabetes Database (ODD), a population-based DM database derived from administrative health records (i.e., NDSS methodology), to a matched cohort of non-DM cases, those with DM were at increased risk for cardiovascular events, nephropathy, amputation, ophthalmic complications, and for death within 10 years of diagnosis.[4] The authors assumed a case to be newly diagnosed if there were no administrative records with a DM code in the preceding three years.[4] Both the accuracy and completeness of the date of diagnosis measure are at risk due to limitations inherent to administrative data. First, the accuracy of this measure if highly dependent on the accuracy of the diagnostic codes recorded on physicians' billing claims. A study involving self-report data from the 1996/97 Ontario Health Survey (a supplement to the National Population Health Survey) and administrative-based data from ODD found that 53.2% of DM cases identified through the ODD did not report having the disease when responding to the Ontario Health Survey.[15] Also there are a limited number of fields for recording diagnostic codes, forcing physicians to be selective in which codes are or are not recorded. The completeness of this measure is also at risk as physicians increasingly are receiving remuneration through alternative payment

structures that do not necessitate the submission of billing claims in order to receive payment.

Although DM is associated with excess morbidity and premature mortality, the long-term prognosis of DM cases has improved over time. Specifically, people with DM are living longer. Using 10 years of data from the ODD, Liscombe et al.[16] reported that age-adjusted and sex-adjusted all-cause death rates among estimated DM cases 20 years of age or older decreased from 17.6/1,000 in 1995 to 13.3/1,000 in 2005. In Nova Scotia, the age-standardized mortality rate for fiscal year 2008/09 was 11.8/1,000 among the adult population with DM (type 1 and type 2 combined) compared to 6.6/1,000 for the population without DM.[3] From 2004/05 to 2008/09, the all-cause mortality rate ratio between those with and without DM remained stable, with the diabetes population dying at twice the rate as those without DM.[3]

There is a large body of literature that examines the impact of DM on other disease processes, but relatively little literature that examines the trajectory of DM alone or DM complicated by other comorbidities. For example, using 15 years of administrative data, a study of Saskatchewan adults over the age of 20 with peripheral arterial disease (PAD) revealed that concurrent DM was associated with increased risk for myocardial infarction, ischemic stroke, and death.[17] In this study, PAD patients with comorbid DM had a mean survival time of 5.6 years compared to 9.6 years for those without comorbid DM. As a result of using administrative data to identify DM cases, some will be false positives and others will be false negatives. In the first years, these false positive and false negative cases may balance out. Over time, however, false positive cases accumulate because the cases definition rules people in, but it does not rule people out.

A national comparison of mortality files from Statistics Canada revealed that mortality rates due to DM (i.e., underlying cause) vary across provinces. Age-standardized mortality rates from DM were highest in Newfoundland and Labrador for both men and women at 54.7 and 53.4 per 100,000 population and lowest in Alberta for males and in British Columbia for females at 31.1 and 22.4 per 100,000 population respectively.[18] Hu et al. found that on average, mortality due to DM increased gradually across the 15-year study period (1986-2000); the average annual increase was higher for males than for

females at 2.4% and 0.7% respectively. The authors cautioned that their results under-represent the true burden of DM because DM is known to be under-reported as the underlying cause of death on death certificates.[18] The authors also noted that their study was limited in that they could not differentiate between type 1 and type 2 DM.[18]

Rationale

It is difficult to understand the survival of persons with DM when we still do not have a clear understanding of how to count the actual number of DM cases with any degree of reliability. Much of the Canadian literature relies on administrative health records to ascertain cases of DM.[3,4,16,17] Although an important first step in understanding DM in Canada, these studies are limited in that DM cases are not clinically confirmed and there is no way to adequately distinguish between type 1 and type 2 cases or assign a true date of diagnosis. These factors limit our ability to understand the trajectory of DM from onset, to diagnosis, complications, and ultimately to death.

Nova Scotia is uniquely positioned within Canada as a site for conducting population-based DM research pertaining to the burden of DM. The rich population-based Registry of over 75,000 clinically confirmed DM/prediabetes cases maintained by the DCPNS overcomes many of the identified limitations of existing DM data sources. It contains longitudinal records for clinically confirmed DM cases that permit the identification of exact date of DM diagnosis, comorbidities present at time of initial DC visit, approximate date of diagnosis for subsequent comorbidities (for a subset of the population), and current information about date of death. Together, these factors provide an unprecedented opportunity to explore the factors associated with survival for a large population-based cohort of clinically confirmed cases of DM.

Objectives

Data from the DCPNS Registry were used to examine factors associated with survival (i.e., from date of birth to date of death/end of study period) for a cohort of clinically confirmed type 1 and type 2 DM cases. Specifically,

1. Type 1 and type 2 DM cases were described in terms of sex, DHA of care, comorbidity status (hypertension and/or dyslipidemia) at first DC visit, and survival

2. Differences in survival by comorbidity status at first DC visit were explored separately for type 1 and type 2 DM cases while controlling for age at DM diagnosis, age at first DC visit, sex, and DHA of care

CHAPTER 2: METHODOLOGY

Study Design

Through this observational study, a historical cohort of clinically confirmed DM cases was followed prospectively from date of first DC visit until date of death or until the end of the study period. Secondary analyses of data collected through the DCPNS Registry were conducted in an effort to understand factors associated with survival in this population.

This study was approved by the Dalhousie University Research Ethics Board.

Data Source

As of March 31, 2009, the DCPNS Registry held records for over 300,000 visits made by approximately 75,000 new referrals to Nova Scotia DCs from January 1st, 1992 onward for paediatric cases (< 19 years) and April 1st, 1994 onward for adult cases (≥ 19 years).

The earliest DCs in NS were operating in 1960s – long before the existence of the DCPNS Registry. When the Registry was first established, historical information for existing DC cases was entered and information for newly referred patients was collected at the time of the patient's first DC visit following referral (some patients can be re-referred, thus can have multiple records). This information was abstracted centrally, by DCPNS staff, from a standardized Physician Referral Form (see Appendix B) used by all referring physicians in the province. This form includes a section for basic demographics, date of diagnosis, DM type, medication history, and the presence of other medical problems as well as an overview of current diagnostic criteria, treatment targets, and recommendations for DM management. The DCPNS periodically revises this form to reflect changes in clinical practice guidelines. The opportunity to correct erroneous information and update missing fields was limited for patients with records entered only at the time of first DC visit due to the centralized entry.

Starting in 2002, the DCPNS Registry evolved to collect longitudinal data via the installation of the On-site (computerized) DCPNS Registry within DCs. By 2010, all

DHAs in the province were equipped with the On-site DCPNS Registry. Now, information from the Physician Referral Form is entered locally, by DC staff, into the On-site DCPNS Registry. They also enter information pertaining to DC encounters and indicators of care abstracted from a standardized Patient Flow Sheet used by all DCs in the province (see Appendix C). This form includes sections for DM type, clinical measures (e.g., height, weight, blood pressure, glycated haemoglobin [A1C], lipids, etc.), DM treatment, and use of medication to control blood glucose, blood pressure, and lipids. With the implementation of longitudinal data collection through the On-site DCPNS Registry, the opportunity to correct or update records was greatly enhanced.

In 2008, the DCPNS Registry started to receive laboratory information for Registry cases through an interface with the Laboratory Information System. As of 2010, lab data for all DCs from DHAs 1-8 were entered into the DCPNS Registry directly through this interface, reducing data entry burden for DC staff. A similar interface for DHA 9 and the Izaak Walton Killam (IWK) Health Centre is pending.

There are several checks in place to ensure that the data held in the DCPNS Registry are accurate. The Registry software has a built-in check to prevent the entry of out-of-range values for a number of fields (e.g., health card number, weight, etc.). Data from all DCs are merged and additional quality checks are run. Sex, date of birth, and date of death are checked against the Medical Services Insurance (MSI) Registry file held by Medavie Blue Cross, and frequencies are calculated to determine if there are outliers or unusual data. The DCPNS also follows up with each DC to confirm DM type for all newly diagnosed paediatric cases. Reports of any suspected errors are sent to the originating DCs for correction. Moreover, DC staff use the DCPNS Registry to monitor patient management; thus, there is an imperative to enter accurate and complete data.

Study Population

As of March 31, 2009, the DCPNS Registry contained 75,081 records for clinically confirmed DM/prediabetes cases receiving care from the province's DCs including members of the Canadian Armed Forces and RCMP as well as a limited number of out-of-province patients. As such, the study population is representative of DM cases

attending NS DCs rather than all DM cases diagnosed in the province. It is estimated, however, that at least 70% of DM cases in NS attend a DC at least once. Furthermore, when the DCPNS Registry was first established, records were entered for long-standing DC cases; thus, entry into the study population was predicated on surviving until the Registry was established. Information about DM cases whom died prior to the Registry being established was not entered into the Registry.

The study population was limited to type 1 and type 2 DM cases with a valid Nova Scotia health card number (N=59,229). Members of the Armed Forces and RCMP were excluded as the mobile nature of this population could bias the results through differential ascertainment of the outcome variable. Cases with GDM only were excluded as GDM is not a chronic condition but rather a transitory condition that resolves with parturition. Cases with other specific types of DM were excluded as the underlying aetiology of their DM (genetic mutations, drug use, or other disease processes) could differentially affect the outcome variable. The study population was restricted to cases for whom a date of DM diagnosis was recorded (N=53,472), sex was recorded (N=53,471), and for whom no illogical date sequences existed (e.g., DC visit after date of death; N=53,278).

The classification of DM is not necessarily a straight forward process and may require additional blood tests (e.g., presence of pancreatic islet antibodies) to distinguish between type 1 and type 2 DM.[7] As such, it is possible for a DCPNS Registry cases to have some records with type 1 recorded and other records with type 2 recorded. To account for any potential misclassification of DM type, type 1 cases were restricted to those diagnosed between 6 months and 20 years and type 2 cases were restricted to those diagnosed at 8 years of age and older (N= 52,056). Cases with ambiguous DM type (e.g., both type 1 and type 2) or improbable treatment sequences (e.g., insulin followed by diet only) were excluded as were cases with an improbable sequence of comorbidity (e.g., hypertension at first visit but not at last visit) leaving a final study population of N=50,017 (N=2,043 type 1s and N=47,974 type 2s).

Study Measures

Diabetes type

Because type 1 and type 2 DM have different underlying aetiology, DM type as recorded in the DCPNS Registry was used as a stratification variable.

Assessment of comorbidity

Comorbidity status was based on the presence of hypertension and/or dyslipidemia at first DC visit; the four levels of the variable were neither, hypertension alone, dyslipidemia alone, and both hypertension and dyslipidemia. Anyone with a medical problem of hypertension and/or taking a antihypertensive medication, and/or with two blood pressure measures $\geq$ 140/90 by their first type 1 or type 2 DC visit was deemed to have hypertension. Anyone with a medical problem of dyslipidemia and/or taking a lipid lowering medication, and/or with a single low-density lipoprotein cholesterol (LDL-C) measure $\geq$ 2 by their first type 1 or type 2 DC visit was deemed to have dyslipidemia.

Assessment of mortality

Date of death is captured in the DCPNS Registry and verified against the MSI Registry twice a year. The MSI Registry receives weekly updates from Nova Scotia Vital Statistics. Survival was defined as date of birth to 1) date of death or 2) end of study period (2009-03-31).[19,20] Time from diagnosis to death is often used as the measure of survival; however, this measure of survival is inextricable intertwined with age at diagnosis. Individuals diagnosed later in life have a shorter period of time available to survive. Using birth as the start point eliminated this problem.

Covariates

Individual trajectories from disease onset, to diagnosis, DC referral, and first DC visit are highly variable (see Figure 2.1). As such, it was necessary to control for both age at diagnosis and age at first type 1 or type 2 DC visit.

Figure 2.1:   Possible disease trajectories for type 1 and type 2 diabetes cases
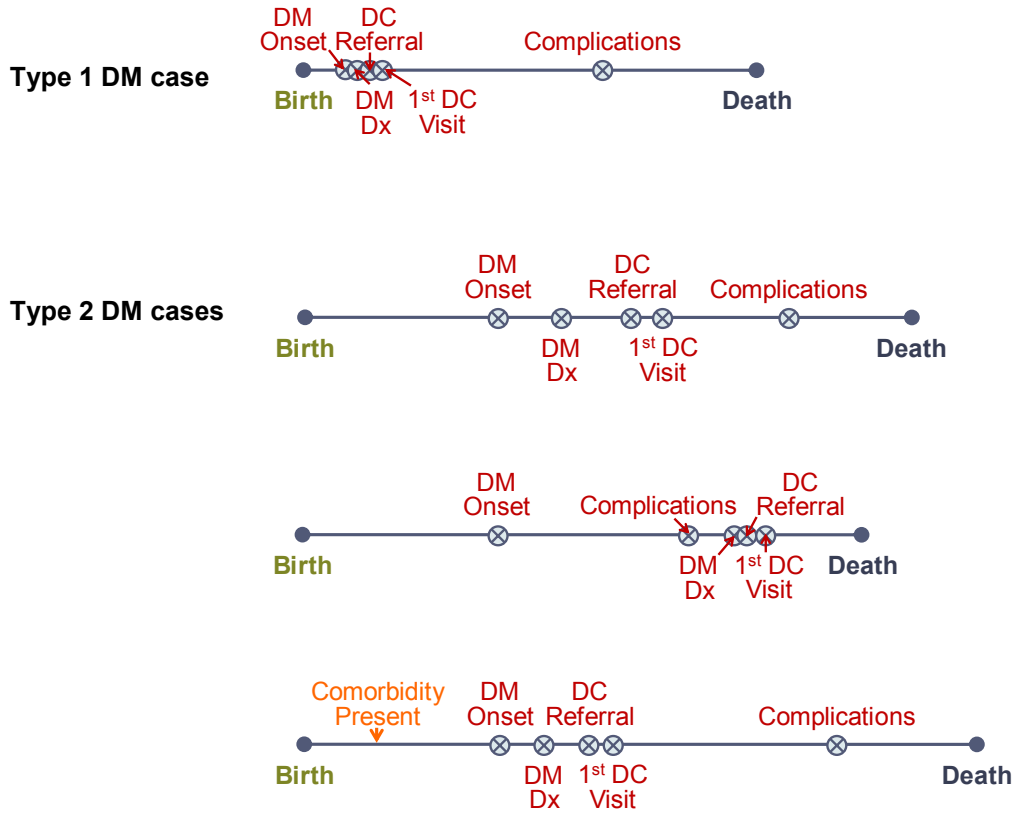
Other covariates included sex and DHA of care based on location of DC. In Nova Scotia, there are nine DHAs plus the IWK Health Centre (see Figure 2.2) – these were collapsed into following four categories: Rural (DHAs 1-7), Cape Breton (DHA 8), Urban (DHA 9 and IWK), and Multiple DHAs (i.e., patient received care from DCs in two or more districts).

Figure 2.2:   District Health Authority (DHA) boundaries

DHA 1: South Shore Health

DHA2: South West Health

DHA3: Annapolis Valley Health

DHA4: Colchester East Hants Health Authority

DHA5: Cumberland Health Authority

DHA6: Pictou County Health Authority

DHA7: Guysborough Antigonish Strait Health Authority

DHA8: Cape Breton Health Authority

DHA9: Capital Health

IWK: Izaak Walton Killam Health Centre
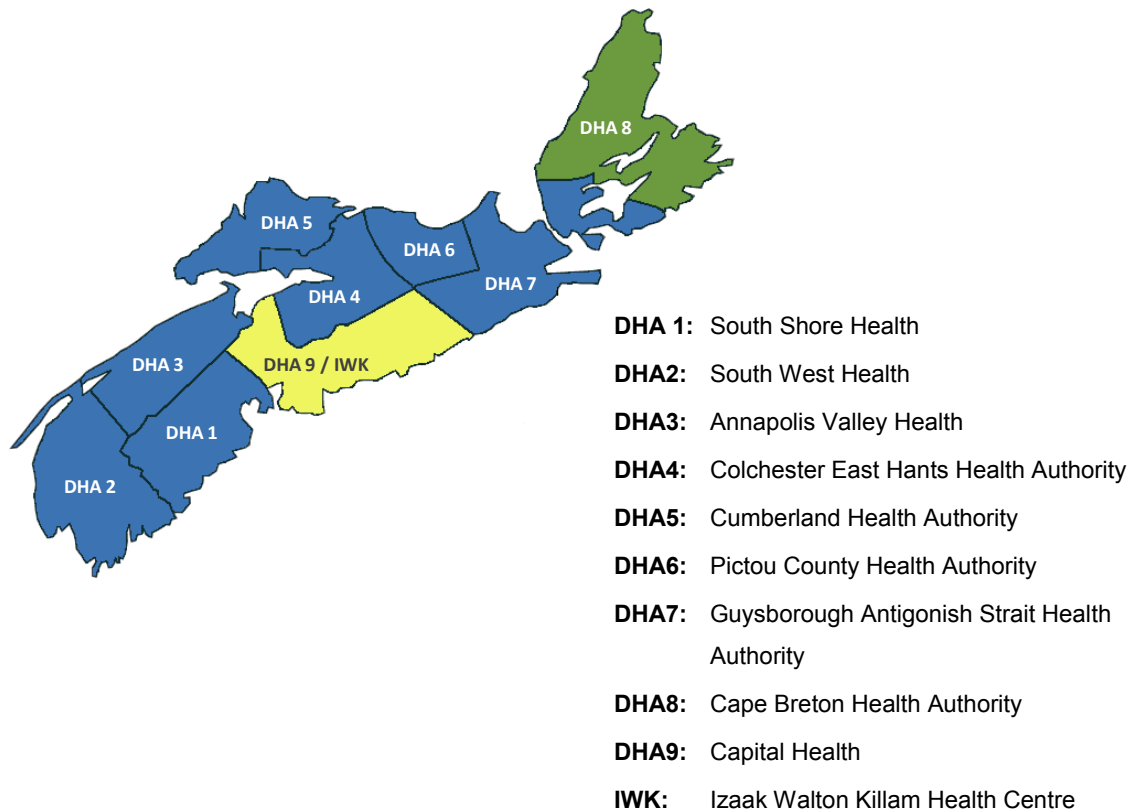
Analyses

All analyses were stratified by DM type.

A variety of descriptive statistics were computed to describe the cohort of clinically confirmed DM cases. Frequencies and percentages were calculated for categorical variables like sex, DHA of care, and comorbidity status. Means and medians were calculated for continuous variables such as survival time, age at diagnosis, and age at first DC visit.

Kaplan Meier curves and log-rank statistics were computed to explore differences in survival for DM cases by sex, DHA of care, and comorbidity status.

Hazard rate ratios (HRRs) and associated 95% confidence intervals were calculated for each of the explanatory variables using Cox Proportional Hazard models. In the context of this study, an HRR greater than one is a measure of the excess risk of mortality

associated with a given characteristic. For example, if the HRR for males (versus females) is two, the mortality rate among males is twice as high as the mortality rate among females.

Cox Proportional Hazard models were constructed for each variable of interest (sex, DHA of care, and comorbidity status) while controlling for age at diagnosis and age at first DC visit (allows for the variability in individual trajectories from disease onset to diagnosis and first DC visit).

To explore the nature of the relationship between comorbidity status and survival, each demographic variable was paired with comorbidity status, and then both demographic variables were combined with comorbidity status. Age at diagnosis and age at first DC visit were included in all models.

All analyses were performed using PASW 18.0 for Windows (SPSS), IBM Corporation, Armonk, New York.

CHAPTER 3:   DIFFERING PATTERNS OF SURVIVAL AMONG CLINICALLY CONFIRMED TYPE 1 AND TYPE 2 DIABETES CASES IN NOVA SCOTIA, CANADA

This manuscript reflects the collective work of Pamela J. Talbot (student), Dr. Jennifer Payne (supervisor), Dr. George Kephart (co-supervisor), and Ms. Peggy Dunbar (Program Manager, Diabetes Care Program of Nova Scotia). Ms. Talbot made substantive intellectual contributions to the study concept and design; the preparation, analyses, and interpretation of the data; and the drafting and revision of this manuscript.

Abstract

Objectives: Limitations underlying much of the epidemiological literature pertaining to the nature and course of diabetes mellitus (DM) restrict our ability to understand the progression of DM from disease onset to death. Data from the Diabetes Care Program of Nova Scotia (DCPNS) Registry were used to examine factors associated with survival for a cohort of clinically confirmed type 1 and type 2 DM cases.

Methods: Historical cohorts of 2,043 type 1 and 47,974 type 2 DM cases were followed from first Diabetes Centre (DC) visit until death/study end. Kaplan Meier curves were computed to explore differences in survival by sex, district health authority (DHA) of care, and comorbidity status. Cox proportional hazard models were used to explore differences in survival by comorbidity status while controlling for other variables.

Results: Median lifespan for type 1 DM cases was 12 years shorter than for type 2 cases. The hazard rate ratios (HRRs) for type 1 cases with dyslipidemia, hypertension, or both compared to those with no comorbidities were 1.63, 2.57, and 7.52 respectively. The HRRs for type 2 cases with dyslipidemia, hypertension, or both compared to those with no comorbidities were 0.95, 1.15, and 1.00 respectively.

Conclusion: Disease progression and the relationship between comorbidity status and survival differed markedly for the type 1 and type 2 DM populations underscoring the need to examine these populations separately. Comorbidity status was intertwined with DM diagnosis and progression among the type 2 DM population but not among the type 1 population.

Introduction

Diabetes mellitus (DM) is associated with an array of micro- and macro-vascular complications and an increased risk for death. However, our understanding of survival (i.e., the trajectory from birth, to DM diagnosis, to the development of comorbidities, and eventually to death) is not well understood due to limitations with existing data sources. A key limitation underlying much of the Canadian DM literature is the ascertainment of true DM cases with a known date of diagnosis and DM type. Moreover, the burden of DM varies across jurisdictions so information from one jurisdiction may not generalise to another. As such, it is important to examine DM and associated factors at the local level.

Nova Scotia is unique in Canada in that the Diabetes Care Program of Nova Scotia (DCPNS) maintains a population-based Registry (DCPNS Registry) of clinically confirmed DM cases attending the province's 39 Diabetes Centres (DCs) that includes basic demographics, exact date of DM diagnosis, DM type, and comorbidities present at time of first DC visit. These data were used to examine factors associated with survival among the type 1 and type 2 DM populations attending Nova Scotia DCs.

Methods

A historical cohort of clinically confirmed DM cases was followed from date of first DC visit until date of death or 2009-03-31. Secondary analyses of data collected through the DCPNS Registry were conducted in an effort to understand factors associated with survival in this population.

This study was approved by the Dalhousie University Research Ethics Board.

Data Source

The DCPNS Registry holds records for over 300,000 visits made by approximately 75,000 new referrals to Nova Scotia DCs from January 1st, 1992 onward for paediatric cases (< 19 years) and April 1st, 1994 onward for adult cases (≥ 19 years). At first, information was collected *only* at the time of a patient's first visit following referral to the DC from a standardized Physician Referral Form that includes basic demographics,

date of diagnosis, DM type, medication history, and the presence of other medical problems. Starting in 2002, the DCPNS Registry evolved to collect longitudinal data abstracted from a standardized Patient Flow Sheet that includes sections for DM type, clinical measures (e.g., height, weight, blood pressure, glycated haemoglobin [A1C], lipids, etc.), DM treatment, and use of medication to control blood glucose, blood pressure, and lipids.

Study population

As of March 31, 2009, the DCPNS Registry contained 75,081 records for clinically confirmed DM/prediabetes cases receiving care from the province's DCs. As such, the study population is representative of DM cases attending NS DCs rather than all DM cases diagnosed in the province.

The study population was limited to type 1 cases diagnosed between 6 months and 20 years and type 2 DM cases diagnosed at 8 years of age and older. Cases were excluded if they were members of the Armed Forces and RCMP or had an invalid or out-of-province health card number; illogical date, diagnostic, or treatment sequences; or missing data in the date of DM diagnosis or sex field. The final study population included 2,043 type 1 and 47,974 type 2 cases.

Study Measures

DM type as recorded in the DCPNS Registry was used as a stratification variable.

Comorbidity status was based on presence of hypertension and/or dyslipidemia *at first DC visit*; the four levels of the variable were neither, hypertension alone, dyslipidemia alone, and both hypertension and dyslipidemia. Anyone with a medical problem of hypertension and/or taking an antihypertensive medication, and/or with two blood pressure measures $\geq$ 140/90 by their first DC visit was deemed to have hypertension. Anyone with a medical problem of dyslipidemia and/or taking a lipid lowering medication, and/or with a single low-density lipoprotein cholesterol (LDL-C) measure $\geq$ 2 by their first DC visit was deemed to have dyslipidemia.

Survival was defined as date of birth to date of death or end of study (2009-03-31).

Covariates included age at diagnosis, age at first DC visit, sex, and District Health Authority (DHA) of care. Nova Scotia has nine DHAs plus the Izaak Walton Killam (IWK) Health Centre – these were collapsed into four categories: Rural (DHAs 1-7), Cape Breton (DHA 8), Urban (DHA 9 and IWK), and Multiple DHAs (i.e., received care in ≥ 2 districts).

Analyses

For each explanatory variable, Kaplan Meier curves were computed to explore differences in survival; log rank tests were performed to test whether the differences were significant. Hazard rate ratios (HRRs) and associated 95% confidence intervals were calculated for each of the explanatory variables using Cox Proportional Hazard models. A series of HRRs were computed for each explanatory variable, controlling for age at diagnosis and age at first DC visit, then for each pair of explanatory variables, and finally for a model containing all explanatory variables. All analyses were performed using PASW 18.0 for Windows (SPSS), IBM Corporation, Armonk, New York.

Results

Characteristics of type 1 and type 2 cases are presented in Table 3.1. For type 1 cases, nearly 20% of the deaths occurred by 30 years of age. For type 2 cases, just over 20% of deaths occurred by 65 years of age.

The median survival for type 1 and type 2 DM cases was 74.1 years and 86.5 years respectively (see Figure 3.1).

Table 3.1:   Characteristics of type 1 and type 2 diabetes cases

Characteristic		**Type 1 (N=2.043)**		**Type 2 (N=47,974)**	
		Number	Percent	Number	Percent
Males		1,033	(50.6%)	25,240	(52.6%)
DHA	Rural (DHA1-7)	475	(23.3%)	23,031	(48.0%)
	Cape Breton (DHA8)	289	(14.1%)	8,869	(18.5%)
	Urban (DHA9 / IWK)	788	(38.6%)	14,997	(31.3%)
	Multiple DHAs	491	(24.0%)	1,077	(2.2%)
Comorbidity status at first Diabetes Centre (DC) visit	None	1,801	(88.2%)	17,175	(35.8%)
	Dyslipidemia only	91	(4.5%)	8,292	(17.3%)
	HTN only	89	(4.4%)	9,023	(18.8%)
	Dyslipidemia & HTN	62	(3.0%)	13,484	(28.1%)
Number (%) deaths		68	(3.3%)	7,295	(15.2%)
		Mean	Median	Mean	Median
Age at DM diagnosis (years)		10.2	10.3	55.6	55.5
Age at first DC visit* (years)		20.1	15.6	58.7	58.7
Age at death (years)		45.1	44.3	74.3	75.7
Person-years of follow-up		28.5	25.9	65.2	65.2

* First DC visit for type 1 or type 2 DM, earlier visits for prediabetes or gestational DM not included

Figure 3.1:   Kaplan Meier curves depicting survival in years by diabetes type
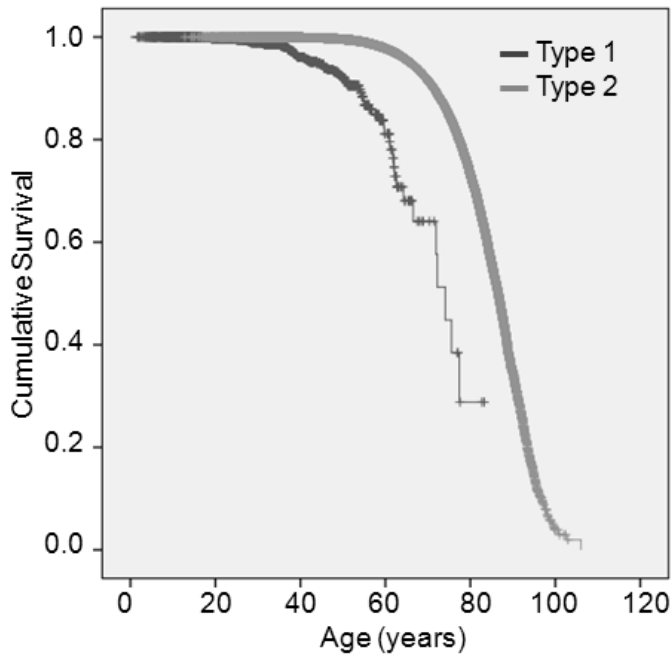
Kaplan Meier curves showed no significant difference in median survival by sex or DHA of care for type 1 cases. There was a significant difference in survival by comorbidity status at time of first DC visit. Median survival for those with hypertension and dyslipidemia was 62.5 years compared to 74.1 years for those with neither comorbidity. Characteristics of type 1 cases by comorbidity status are shown in Table 3.2.

Table 3.2: **Characteristics of type 1 cases by comorbidity status at time of first Diabetes Centre (DC) visit**

Characteristic		Comorbidity status at time of first Diabetes Centre visit							
		Neither (N=1,801)		Dyslipidemia only (N=91)		HTN only (N=89)		Dyslipidemia and HTN (N=62)	
		N	%	N	%	N	%	N	%
Males		918	(51.0%)	49	(53.8%)	40	(44.9%)	26	(41.9%)
DHA	Rural (DHA1-7)	393	(21.8%)	31	(34.1%)	23	(25.8%)	28	(45.2%)
	Cape Breton (DHA8)	257	(14.3%)	n/a	n/a	16	(18.0%)	n/a	n/a
	Urban (DHA9 / IWK)	681	(37.8%)	43	(47.3%)	37	(41.6%)	27	(43.5%)
	Multiple DHAs	470	(26.1%)	n/a	n/a	13	(14.6%)	n/a	n/a
Number (%) deaths		38	(2.1%)	5	(5.5%)	11	(12.4%)	14	(22.6%)
		Mean	Median	Mean	Median	Mean	Median	Mean	Median
Age at diagnosis (years)		10.0	10.1	11.9	12.6	11.4	11.7	10.4	10.5
Age at first type 1 DC visit (years)		17.7	14.0	35.2	37.3	37.6	35.7	41.9	42.0
Age at death (years)		41.7	38.5	55.0	49.2	49.1	44.7	47.3	45.5
Person-years of follow-up		26.4	23.7	41.6	43.8	45.7	45.1	46.7	47.4

n/a – Small cell count, number suppressed

Cox regression models revealed that comorbidity status at time of first DC visit was independently associated with survival (see Table 3.3). The relationship between comorbidity status and survival was not confounded by sex and/or DHA of care as the HRRs for comorbidity status did not vary across the different models.

Approximately 57% of deaths among type 1 DM cases occurred at 40 years of age or later suggesting deaths were more prevalent among cases that entered the DCPNS Registry for the first time at older ages (e.g., long standing DC cases when the Registry was established or long-standing type 1 cases new to the province). Restricting the analyses to newly diagnosed type 1 cases (i.e., diagnosed within one year of first DC visit) would have corrected for this problem. However, by doing so, too few events occurred due to the reduced follow-up time among this young cohort.

To yield more meaningful results, Cox regression models were constructed for type 1 DM cases conditional on survival until age 30, 40 and 50 years (see Table 3.4). These models revealed that comorbidity status at time of first DC visit was independently associated with survival, but the effect attenuated with increased age (i.e., as individuals survived to increasingly older age deciles [conditional survival], the effect for comorbidity status decreased).

Table 3.3: **Hazard rate ratios for comorbidity status among type 1 diabetes cases**

		Models 1a-c	Models 2a-b (a)	Models 2a-b (b)	Model 3 Full Model
(a) Sex	Female	1.00	1.00		1.00
	Male	1.50 (0.92, 2.45)	1.46 (0.90, 2.37)		1.45 (0.89, 2.36)
(b) DHA of care	Rural (DHA1-7)	1.00		1.00	1.00
	Cape Breton (DHA8)	1.18 (0.55, 2.51)		1.32 (0.62, 2.82)	1.31 (0.61, 2.82)
	Urban (DHA9 / IWK)	1.08 (0.61, 1.93)		1.08 (0.60, 1.93)	1.08 (0.60, 1.94)
	Multiple DHAs	0.94 (0.41, 2.15)		0.94 (0.41, 2.17)	0.99 (0.43, 2.27)
(c) Comorbidity Status at first DC visit	Neither	1.00*	1.00*	1.00*	1.00*
	Dyslipidemia alone	1.64 (0.62, 4.35)	1.64 (0.62, 4.35)	1.63 (0.61, 4.32)	1.63 (0.62, 4.32)
	HTN alone	2.59 (1.26, 5.32)	2.62 (1.27, 5.38)	2.55 (1.23, 5.27)	2.57 (1.24, 5.30)
	Dyslipidemia & HTN	7.33 (3.52, 15.3)	7.35 (3.49, 15.5)	7.50 (3.59, 15.7)	7.52 (3.57, 15.8)

* Significant main effect ($p < 0.05$)

Models 1a-c: (a) Sex
    (b) DHA
    (c) Comorbidity status at first type 1 DC visit

Models 2a-b: (a) Comorbidity status at first type 1 DC visit and sex
    (b) Comorbidity status at first type 1 DC visit and DHA

Model 3:   Comorbidity status at first type 1 DC visit, sex, and DHA

Note: All models controlled for age at diagnosis and age at first type 1 DC visit

Table 3.4:   Hazard rate ratios for comorbidity status among type 1 diabetes cases surviving until age 30, 40, and 50 years

		All ages (N=2,043)	Conditional on survival until age		
			Age 30 (N=829)	Age 40 (N=454)	Age 50 (N=202)
(a) Sex	Female	1.00	1.00	1.00	1.00
	Male	1.45 (0.89, 2.36)	1.62 (0.95, 2.77)	1.46 (0.77, 2.79)	1.33 (0.59, 2.99)
(b) DHA of care	Rural (DHA1-7)	1.00	1.00	1.00	1.00
	Cape Breton (DHA8)	1.31 (0.61, 2.82)	1.36 (0.59, 3.16)	1.67 (0.62, 4.46)	0.96 (0.26, 3.61)
	Urban (DHA9 / IWK)	1.08 (0.60, 1.94)	1.11 (0.59, 2.08)	1.30 (0.61, 2.76)	0.80 (0.31, 2.06)
	Multiple DHAs	0.99 (0.43, 2.27)	1.31 (0.51, 3.36)	1.56 (0.44, 5.52)	1.14 (0.25, 5.22)
(c) Comorbidity Status at first DC visit	Neither	1.00*	1.00*	1.00*	1.00
	Dyslipidemia alone	1.63 (0.62, 4.32)	1.79 (0.67, 4.79)	2.12 (0.76, 5.90)	1.22 (0.26, 5.69)
	HTN alone	2.57 (1.24, 5.30)	2.79 (1.33, 5.86)	2.05 (0.82, 5.14)	1.74 (0.57, 5.32)
	Dyslipidemia & HTN	7.52 (3.57, 15.8)	7.54 (3.43, 16.6)	5.55 (2.17, 14.2)	3.29 (1.08, 10.0)

* Significant main effect ($p < 0.05$)
All models include comorbidity status at first type 1 DC visit, sex, and DHA, controlling for age at diagnosis and age at first type 1 DC visit

Kaplan Meier curves showed a significant difference in median survival by sex, DHA of care, and comorbidity status at time for first DC visit for type 2 cases (p-values < 0.01). Median survival was 84.4 and 88.2 years for males and females, respectively. Median survival for cases receiving care from DCs in rural DHAs was 87.0 years compared to 85.7 years for those receiving care in Cape Breton DCs. Median survival of those with hypertension and dyslipidemia was 87.7 years compared to 86.0 years for those with neither comorbidity and 86.3 years for those with hypertension or dyslipidemia alone. Characteristics of type 2 cases by comorbidity status are shown in Table 3.5.

Table 3.5: **Characteristics of type 2 cases by comorbidity status at time of first Diabetes Centre (DC) visit**

		Comorbidity status at time of first Diabetes Centre visit							
		Neither (N=17,175)		Dyslipidemia only (N=8,292)		HTN only (N=9,023)		Dyslipidemia and HTN (N=13,484)	
Characteristic		N	%	N	%	N	%	N	%
Males		9,358	(54.5%)	4,665	(56.3%)	4,327	(48.0%)	6,890	(51.1%)
DHA	Rural (DHA1-7)	8,248	(48.0%)	3,979	(48.0%)	4,613	(51.1%)	6,191	(45.9%)
	Cape Breton (DHA8)	3,871	(22.5%)	1,239	(14.9%)	1,632	(18.1%)	2,127	(15.8%)
	Urban (DHA9 / IWK)	4,528	(26.4%)	2,904	(35.0%)	2,605	(28.9%)	4,960	(36.8%)
	Multiple DHAs	528	(3.1%)	170	(2.1%)	173	(1.9%)	206	(1.5%)
Number (%) deaths		2,949	(17.2%)	816	(9.8%)	2,059	(22.8%)	1,471	(10.9%)
		Mean	Median	Mean	Median	Mean	Median	Mean	Median
Age at diagnosis (years)		53.8	53.6	53.5	53.3	58.7	58.4	57.3	57.2
Age at first type 1 DC visit (years)		56.7	56.8	55.9	55.7	61.9	61.9	60.6	60.4
Age at death (years)		74.2	75.6	71.2	72.0	76.5	77.8	73.3	74.7
Person-years of follow-up		64.3	64.5	62.1	62.0	69.2	69.6	65.7	65.6

Cox regression models showed that sex, DHA of care, and comorbidity status at time of first DC visit were independently associated with survival (see Table 3.6). The relationship between comorbidity status and survival was not confounded by sex and/or DHA of care as the HRRs did not vary across the different models.

Individual trajectories from diagnosis, DC referral, and first DC visit are highly variable and could impact survival. To reduce some of this variability, the cohort was restricted to type 2 cases diagnosed within one year of their first DC visit. Restricting the cohort in this way had virtually no effect on the HRRs.

Being diagnosed with DM at progressively older ages can impact survival. First, surviving long enough to be diagnosed at an older age may indicate that an individual is in generally good health (i.e., healthy survival effect). Alternatively, the probability of an individual having a comorbidity at the first DC visit increases with increased age at DM diagnosis. To understand better the impact of age at DM diagnosis on survival, the cohort was restricted to type 2 cases diagnosed at 40, 50, 60, or 70 years of age or older. Restricting the cohort in this way had little effect on the HRRs (see Table 3.7).

Table 3.6:   Hazard rate ratios for comorbidity status among type 2 diabetes cases

		Models 1a-c	Models 2a-b (a)	Models 2a-b (b)	Model 3 Full Model
(a) Sex	Female	1.00*	1.00*		1.00*
	Male	1.58 (1.51, 1.66)	1.59 (1.52, 1.67)		1.59 (1.52, 1.67)
(b) DHA of care	Rural (DHA1-7)	1.00*		1.00*	1.00*
	Cape Breton (DHA8)	1.14 (1.07, 1.21)		1.14 (1.07, 1.21)	1.15 (1.08, 1.22)
	Urban (DHA9 / IWK)	1.05 (0.99, 1.11)		1.05 (0.99, 1.11)	1.04 (0.98, 1.10)
	Multiple DHAs	0.64 (0.53, 0.77)		0.64 (0.53, 0.77)	0.64 (0.53, 0.77)
(c) Comorbidity Status at first DC visit	Neither	1.00*	1.00*	1.00*	1.00*
	Dyslipidemia alone	0.94 (0.87, 1.02)	0.95 (0.88, 1.03)	0.94 (0.87, 1.02)	0.95 (0.88, 1.03)
	HTN alone	1.11 (1.05, 1.17)	1.15 (1.09, 1.22)	1.11 (1.05, 1.17)	1.15 (1.09, 1.22)
	Dyslipidemia & HTN	0.95 (0.89, 1.01)	1.00 (0.94, 1.06)	0.95 (0.89, 1.02)	1.00 (0.94, 1.07)

* Significant main effect ($p < 0.05$)

Models 1a-c: (a) Sex
      (b) DHA
      (c) Comorbidity status at first type 2 DC visit
Models 2a-b:(a) Comorbidity status at first type 2 DC visit and sex
      (b) Comorbidity status at first type 2 DC visit and DHA
Model 3:   Comorbidity status at first type 2 DC visit, sex, and DHA
Note: All models controlled for age at diagnosis and age at first type 2 DC visit

Table 3.7: **Hazard rate ratios for comorbidity status among type 2 diabetes cases diagnosed at age 40, 50, 60, or 70 years of age or older**

		All ages (N=47,974)	Conditional on being diagnosed at or after			
			Age 40 (N=42,347)	Age 50 (N=31,890)	Age 60 (N=17,690)	Age 70 (N=7,076)
(a) Sex	Female	1.00*	1.00*	1.00*	1.00*	1.00*
	Male	1.59 (1.52, 1.67)	1.60 (1.52, 1.67)	1.62 (1.54, 1.71)	1.61 (1.51, 1.70)	1.53 (1.41, 1.66)
(b) DHA of care	Rural (DHA1-7)	1.00*	1.00*	1.00*	1.00*	1.00
	Cape Breton (DHA8)	1.15 (1.08, 1.22)	1.14 (1.07, 1.21)	1.14 (1.06, 1.21)	1.09 (1.01, 1.17)	1.08 (0.97, 1.19)
	Urban (DHA9 / IWK)	1.04 (0.98, 1.10)	1.04 (0.98, 1.10)	1.02 (0.96, 1.09)	0.99 (0.93, 1.07)	0.97 (0.88, 1.06)
	Multiple DHAs	0.64 (0.53, 0.77)	0.62 (0.50, 0.75)	0.61 (0.49, 0.77)	0.60 (0.46, 0.79)	0.76 (0.51, 1.13)
(c) Comorbidity Status at first DC visit	Neither	1.00*	1.00*	1.00*	1.00*	1.00
	Dyslipidemia alone	0.95 (0.88, 1.03)	0.95 (0.88, 1.03)	0.96 (0.88, 1.04)	0.97 (0.87, 1.07)	0.90 (0.77, 1.05)
	HTN alone	1.15 (1.09, 1.22)	1.14 (1.08, 1.21)	1.13 (1.07, 1.20)	1.07 (1.00, 1.15)	1.01 (0.92, 1.10)
	Dyslipidemia & HTN	1.00 (0.94, 1.07)	0.98 (0.92, 1.05)	0.97 (0.90, 1.04)	0.95 (0.87, 1.03)	0.90 (0.79, 1.00)

* Significant main effect ($p < 0.05$)

All models include comorbidity status at first type 2 DC visit, sex, and DHA, controlling for age at diagnosis and age at first type 2 DC visit

Discussion

Type 1 and type 2 DM are distinct diseases with different patterns of survival. The percentage of deaths among the type 1 population attending DCs in Nova Scotia was relatively low at 3% (compared to 15% among the type 2 population). Deaths occurred across the age spectrum, with nearly 20% type 1 deaths occurring by 30 years of age. The median survival for this population was 12 years shorter than that of type 2 population. After 40 years, the mortality rate among the type 1 population steadily increased with the maximum age at death being 77 years. For the type 2 population, this increase in mortality did not occur until about age 60, and the maximum age at death was over 100 years. The difference in survival patterns for these two populations reinforces the need to examine them separately.

The Kaplan Meier curves suggest that type 1 cases with no comorbidities at time of first DC visit had the longest survival while the shortest survival was observed among those with both hypertension and dyslipidemia. Compared to type 1 cases with no comorbidities, those with hypertension, dyslipidemia, or both were considerably older at time of first DC visit and were more likely to be female. However, after controlling for age at diagnosis, age at first DC visit, sex, and DHA of care, comorbidity status at time of first DC visit remained a potent risk factor for mortality. The mortality rate for those with hypertension or dyslipidemia was approximately double that of type 1 cases with neither of the comorbidities. Having both comorbidities together was associated with an even greater risk – the mortality rate was more than 7 times higher for type 1 cases with both hypertension and dyslipidemia compared to those with neither comorbidity. This finding is consistent literature regarding metabolic syndrome showing that the impact of multiple comorbid conditions on health is multiplicative rather additive.[21] When analyses were restricted to type 1 cases surviving until age 30, 40, and 50, the multiplicative effect of hypertension and dyslipidemia on survival remained; although, it attenuated with increased age suggesting that there were other competing risks contributing to mortality.

The Kaplan Meier curves depicted that type 2 cases with no comorbidities had the shortest survival while the longest survival was observed among those with both hypertension and dyslipidemia – a complete reversal of the findings for type 1 cases. Age

at time of first DC visit varied by 5 years across the comorbidity groups. The distribution of males versus female was similar for type 2 cases with hypertension or hypertension and dyslipidemia, and approximately 10% more males than females had neither comorbidity or dyslipidemia alone. After controlling for age at diagnosis, age at first DC visit, sex, and DHA of care, the significant association between comorbidity status at time of first DC visit and survival persisted; however, the direction of the relationship changed such that type 2 cases with hypertension alone had a higher mortality rate compared to those with neither comorbidity. When the analyses were restricted to type 2 cases diagnosed within one year of their first DC visit, the effect of comorbidity status on survival was unchanged. Similarly, when the analyses were restricted to type 2 cases diagnosed at 40, 50, 60, or 70 years of age or older, the effect of comorbidity status on survival was unchanged.

The findings for type 2 cases are perplexing as one would expect each of the comorbidities to contribute to increased mortality and the presence of both comorbidities to act synergistically to increase mortality in a multiplicative fashion as with type 1 cases. Several explanations for these puzzling results exist.

For type 1 cases, the time between disease onset and first DC visit is relatively short. Type 1 DM has an acute onset, so there is minimal lag between disease onset and diagnosis, and newly diagnosed type 1 cases in Nova Scotia are typically seen by DC staff within 24-48 hours of diagnosis. As such, very few type 1 cases had comorbidities present at the time of their first DC visit. For type 2 cases, the lag between disease onset and diagnosis can be as long as 12 years.[11] By this time, comorbidities may already be present.[7, 22]

For type 2 DM cases, it is possible that the presence of a comorbidity contributed to earlier detection of DM, thus mitigating against some of the excess mortality.[12] Detecting type 2 DM earlier in the progression of the disease affords the opportunity to delay the onset of complications and death.[23-25] When measuring survival from time of diagnosis to death, early detection can contribute to lead time bias – meaning that survival appears to be longer when in fact the start point was just moved backward. In this study, lead time bias was not a problem, as survival was measured from birth to

death. However, there was no way to control for any additional years of life gained as a result of early DM detection.

It is also possible that type 2 DM cases with additional comorbidities were managed more aggressively by their healthcare providers – especially given the emphasis on the control of hypertension and dyslipidemia following the United Kingdom Prospective Diabetes Study.[23,26] In Nova Scotia, DC staff use the On-site DCPNS Registry to identify and target interventions for those with clinical indicators outside accepted management targets. These high-risk individuals may also been seen more often by other healthcare providers (e.g., family physician, specialist physician, nurse practitioner, etc). Finally, individuals with additional comorbidities may be more motivated to self-manage their disease.

Strengths and limitations

This exploratory work exploited the rich data contained in DCPNS' population-based registry of clinically confirmed DM cases with known DM type, date of diagnosis, and comorbidities present at first DC visit. Some records, especially those from the early years of the Registry, were excluded due to incomplete data. However, it is unlikely that excluding these cases changed the results. When the cohort was restricted to cases entering the DC within one year of diagnosis, the HRRs remained virtually unchanged.

The DCPNS Registry does not capture information about non-attendees of DCs. Although it is estimated that all paediatric DM cases diagnosed in the province since 1992 are represented in the DCPNS Registry, older DM cases are known to be under-represented, especially the frail elderly living in long-term care facilities. Although the issue of generalisability must be acknowledged, it is unlikely that the biological processes associated with DM differ between DC attendees versus non-attendees.

For DM cases entering the DCPNS Registry the year it was established, entry was predicated on surviving until the Registry was established – thus there is left truncation of data. For example, a DM case diagnosed in 1944 who survived beyond age 50 would have been eligible to be captured by the DCPNS Registry as an adult in 1994; however, a DM case diagnosed in 1944 who died at age 40 would not have been eligible to be

captured by Registry in 1994. This left truncation of data likely biased the Kaplan Meier estimates of median survival upward. However, it s unlikely that the hazard rate ratios calculated through Cox proportional hazard models were affected by this artefact of the data.

By combining hypertension and dyslipidemia into a composite variable, it was possible to explore the effects of having one or both comorbidities at the time of first DC visit. This approach mirrors reality – DM seldom occurs in isolation. In Nova Scotia, over 70% of adults (≥ 20 years) with DM also have hypertension.[3] In fact, 11% of Canadians with DM have three or more other chronic conditions.[7] As such, it is important to understand how these conditions work together to affect survival.

In the early years of the Registry, information was entered at time of first visit only; longitudinal data collection was not phased in until 2002. To ensure comparability across the study population with regard to the completeness of comorbidity status information, the comorbidity status variable was ascertained at time of first DC visit *only*. The prevalence of these comorbidities increases with age, meaning that individuals who were diagnosed with DM at older ages would be more likely to have hypertension and/or dyslipidemia at their first DC visit than those who were diagnosed at younger ages. Kaplan Meier procedures does not account for these factors. The Cox proportional hazard models adjusted for age at diagnosis and age at first DC visit; however, this adjustment may not have fully accounted for the impact of measuring comorbidity at time of first DC visit. However, when the type 2 DM cohort was restricted to newly diagnosed cases and cases diagnosed at increasingly older ages, there was no effect on the HRRs.

One aspect of DM, hypertension, and dyslipidemia that this study did not consider was the effect of changing guidelines on survival. In 1998, the clinical threshold for a FPG was reduced from 7.8 to 7.0 mmol/L.[9] Future research needs to explore the effect of this reduction in the diagnostic threshold change on survival as earlier detection of DM offers the opportunity to delay the development of comorbidities and/or death.[23-25] Similarly, the impact of more aggressive management of blood pressure and lipids could be explored.

Summary

In summary, this study highlights the need to examine type 1 and type 2 DM separately – these are different diseases with different trajectories. The fact that comorbidity status was intertwined with DM diagnosis and progression among the type 2 DM population but not among the type 1 population further underscores the need to understand these diseases as separate entities.

CHAPTER 4: CONCLUSION

Process

The premise for this study arose from a larger Public Health Agency of Canada (PHAC)-funded project undertaken by the DCPNS to understand factors associated with the progression of DM among a clinically confirmed cohort of type 1 and type 2 DM cases. A key finding of the larger project was that the notion of disease severity was not a useful concept.[27] Endocrinologists, DC educators, and DC managers noted that clinical values (e.g., A1C, blood pressure), DM type and duration, complications and comorbidities, case complexity, mental health and wellbeing, and social support all play a role in so-called case severity. The only difference between the groups was that endocrinologists placed more emphasis on factors associated with cardiovascular risk whereas DC educators and managers focussed more on the time required to manage a case. Although this term appears frequently in the literature, it lacks a consistent definition.[28-31]

This early work affected the direction of this analysis. Originally, disease severity was to be included as a covariate in Cox proportional hazard models. Instead, components of so-called disease severity were included in the models. The analyses were stratified by DM type. Age at diagnosis was used to account for DM duration. Blood pressure and LDL values as well as medication use were included in the measure of hypertension and dyslipidemia – the two most common comorbidities associated with DM. Although important, measures of mental health and wellbeing and social support were not available for analyses. Similarly, some other important clinical values like A1C and treatment type were not included in the models as they vary over time and the structure of the data would not permit the use of these data as time-varying covariates (i.e., not everyone was measured at the same time).

Key Findings

Type 1 and type 2 DM are distinct diseases with different patterns of survival. The percentage of deaths among the type 1 population attending DCs in Nova Scotia was relatively low at 3% (compared to 15% among the type 2 population). Deaths occurred

across the age spectrum, with nearly 20% type 1 deaths occurring by 30 years of age. The median survival for this population was 12 years shorter than that of type 2 population. After 40 years, the mortality rate among the type 1 population steadily increased with the maximum age at death being 77 years. For the type 2 population, this increase in mortality did not occur until about age 60, and the maximum age at death was over 100 years. The difference in survival patterns for these two populations reinforces the need to examine them separately.

The Kaplan Meier curves depicted that type 1 cases with no comorbidities at time of first DC visit had the longest survival while the shortest survival was observed among those with both hypertension and dyslipidemia. Compared to type 1 cases with no comorbidities, those with hypertension, dyslipidemia, or both were considerably older at time of first DC visit and were more likely to be female. However, after controlling for age at diagnosis, age at first DC visit, sex, and DHA of care, comorbidity status at time of first DC visit remained a potent risk factor for mortality. The mortality rate for those with hypertension or dyslipidemia was approximately double that of type 1 cases with neither comorbidity. Having both comorbidities together was associated with an even greater risk – the mortality rate was more than 7 times higher for type 1 cases with both hypertension and dyslipidemia compared to those with neither comorbidity. This finding is consistent literature regarding metabolic syndrome showing that the impact of multiple comorbid conditions on health is multiplicative rather additive.[21] When analyses were restricted to type 1 cases surviving until age 30, 40, and 50, the multiplicative effect of hypertension and dyslipidemia on survival remained; although, it attenuated with increased age suggesting that there were other competing risks contributing to mortality.

The Kaplan Meier curves depicted that type 2 cases with no comorbidities had the shortest survival while the longest survival was observed among those with both hypertension and dyslipidemia – a complete reversal of the findings for type 1 cases. Age at time of first DC visit varied by 5 years across the comorbidity groups. The distribution of males versus female was similar for type 2 cases with hypertension or hypertension and dyslipidemia, and approximately 10% more males than females had neither comorbidity or dyslipidemia alone. After controlling for age at diagnosis, age at first DC visit, sex, and DHA of care, the significant association between comorbidity status at

time of first DC visit and survival persisted; however, the direction of the relationship changed such that type 2 cases with hypertension alone had a higher mortality rate compared to those with neither comorbidity. When the analyses were restricted to type 2 cases diagnosed within one year of their first DC visit, the effect of comorbidity status on survival was unchanged. Similarly, when the analyses were restricted to type 2 cases diagnosed at 40, 50, 60, or 70 years of age or older, the effect of comorbidity status on survival was unchanged.

The findings for type 2 cases are perplexing as one would expect each comorbidity to contribute to increased mortality and the presence of both comorbidities to act synergistically to increase mortality in a multiplicative fashion as with type 1 cases. Several explanations for these puzzling results exist.

For type 1 cases, the time between disease onset and first DC visit is relatively short. Type 1 DM has an acute onset, so there is minimal lag between disease onset and diagnosis, and newly diagnosed type 1 cases in Nova Scotia are typically seen by DC staff within 24-48 hours of diagnosis. As such, very few type 1 cases had comorbidities present at the time of their first DC visit. For type 2 cases, the lag between disease onset and diagnosis can be as long as 12 years.[11] By this time, comorbidities may already be present.[7,22]

For type 2 DM cases, it is possible that the presence of a comorbidity contributed to earlier detection of DM, thus mitigating against some of the excess mortality.[12] Detecting type 2 DM earlier in the progression of the disease affords the opportunity to delay the onset of complications and death.[23-25] When measuring survival from time of diagnosis to death, early detection can contribute to lead time bias – meaning that survival appears to be longer when in fact the start point was just moved backward. In this study, lead time bias was not a problem, as survival was measured from birth to death. However, there was no way to control for any additional years of life gained as a result of early DM detection.

It is also possible that type 2 DM cases with additional comorbidities were managed more aggressively by their healthcare providers – especially given the emphasis on the control of hypertension and dyslipidemia following the United Kingdom Prospective Diabetes

Study.[23,26] In Nova Scotia, DC staff use the On-site DCPNS Registry to identify and target interventions for those with clinical indicators outside accepted management targets. These high-risk individuals may also been seen more often by other health care providers (e.g., family physician, specialist physician, nurse practitioner, etc). Finally, individuals with additional comorbidities may be more motivated to self-manage their disease.

Strengths and limitations

A key strength of this study was the data source; the DCPNS Registry contains rich data for a large population-based cohort of clinically confirmed cases of DM with known DM type, date of diagnosis, and comorbidities present at first DC visit. Some records, especially those from the early years of the Registry, were excluded due to incomplete data. However, it is unlikely that excluding these cases changed the results. When the cohort was restricted to cases entering the DC within one year of diagnosis, the HRRs remained virtually unchanged.

DCPNS Registry does not capture information about DM cases who do not attend DCs. Although it is estimated that all paediatric DM cases diagnosed in the province since 1992 are represented in the DCPNS Registry, older DM cases are known to be under-represented, especially the frail elderly living in long-term care facilities. Thus, the generalisability of results may be limited. Although the issue of generalisability must be acknowledged, it is unlikely that the biological processes associated with DM differ between DC attendees versus non-attendees. The coverage of the DCPNS Registry would pose more of a problem if the outcome of interest were prevalence and incidence rates.

For DM cases entering the DCPNS Registry the year it was established, entry was predicated on surviving until the Registry was established – thus there is left truncation of data. For example, a DM case diagnosed in 1944 who survived beyond age 50 would have been eligible to be captured by the DCPNS Registry as an adult in 1994; however, a DM case diagnosed in 1944 who died at age 40 would not have been eligible to be captured by Registry in 1994. This left truncation of data likely biased the Kaplan Meier

estimates of median survival upward. However, the hazard rate ratios calculated through Cox proportional hazard models were likely unaffected by this artefact of the data.

By combining hypertension and dyslipidemia into a composite variable, it was possible to explore the effects of having one or both comorbidities. This approach mirrors reality – DM seldom occurs in isolation. In Nova Scotia, over 70% of adults (≥ 20 years) with DM also have hypertension.[3] In fact, 11% of Canadians with DM have three or more other chronic conditions.[7] As such, it is important to understand how these conditions work together to affect survival.

In the early years of the Registry, information was entered at time of first visit only; longitudinal data collection was not phased in until 2002. To ensure comparability across the study population with regard to the completeness of comorbidity status information, the comorbidity status variable was ascertained at time of first DC visit *only*. The prevalence of these comorbidities increases with age, meaning that individuals who were diagnosed with DM at older ages would be more likely to have hypertension and/or dyslipidemia at their first DC visit than those who were diagnosed at younger ages. Kaplan Meier procedures does not account for these factors. The Cox proportional hazard models adjusted for age at diagnosis and age at first DC visit; however, this adjustment may not have fully accounted for the impact of measuring comorbidity at time of first DC visit. However, when the type 2 DM cohort was restricted to newly diagnosed cases and cases diagnosed at increasingly older ages, there was no effect on the HRRs.

One aspect of DM, hypertension, and dyslipidemia that this study did not consider was the effect of changing guidelines on survival. In 1998, the clinical threshold for a FPG was reduced from 7.8 to 7.0 mmol/L.[9] Future research needs to explore the effect of this reduction in the diagnostic threshold change on survival. Theoretically, earlier detection of DM offers the opportunity to delay the development of comorbidities and death.[23-25] Similarly, the impact of more aggressive management of blood pressure and lipids could be explored.

The use of both Kaplan Meier and Cox proportional hazard models allowed for the exploration of difference aspects of survival. Kaplan Meier curves showed the nuances of survival (e.g., did differences in survival occur early on and then attenuate or were they

consistent across the follow-up period) while the Cox models allowed for the assessment of confounding of covariates on the relationship between comorbidity status variable and survival.

Relevance

In Nova Scotia, as in other parts of the county, there is a dearth of information about the nature of survival for DM cases. The results of this research directly address this knowledge gap by providing detailed information about important factors associated with survival for a cohort of clinically confirmed DM cases. This study highlights the need to examine type 1 and type 2 DM separately – these are different disease with different trajectories. The fact that comorbidity status was intertwined with DM diagnosis and progression among the type 2 DM population but not among the type 1 population further underscores the need to understand these diseases as separate entities.

Another benefit of this work is the knowledge gained about the nuances of using DCPNS Registry data for longitudinal research. Prior to the PHAC-funded project, which formed the premise for this work, DCPNS Registry data had not been used in a longitudinal fashion. The DCPNS had completed various projects using serial cross-sections of data, but had not used it to follow individual cases across time. Using the data in this way highlighted some issues that otherwise would not have come to light (e.g., impossible date sequences, illogical sequences of DM or comorbidity, conflicting data between DCs). A few of these issues were simply the result of historical artefacts in the data, especially data collected in the early years of the Registry when the ability to correct/update data fields was limited. However, where the opportunity exists, these learnings will be used by the DCPNS to help guide the development of Registry as it moves to a different platform.

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APPENDIX A

CANADIAN DIABETES ASSOCIATION CLINICAL PRACTICE GUIDELINES (CPGs) FOR DIABETES: 1992, 1998, 2003, AND 2008

CPG	Diagnostic Criteria
1992[1]	Symptoms of diabetes (e.g., increased thirst, polydipsia, polyuria, polyphagia, weight loss, fatigue, blurred vision, etc.) and a random venous plasma glucose >11.1 mmol/L, **OR** Fasting venous plasma glucose (FPG) >7.8 mmol/L on ≥ 2 occasions, **OR** FPG < 7.8 mmol/L but >11.1 mmol/L in a 2h sample and one other sample 0-2hr after a 75g glucose load in 2 glucose tolerance tests In people with no obvious signs of hyperglycaemia, biochemical hyperglycaemia must be confirmed
1998[2]	Symptoms of diabetes (e.g., fatigue, polyuria, polydipsia, unexplained weight loss) plus a casual venous plasma glucose (casual PG) ≥11.1 mmol/L, **OR** FPG ≥7.0 mmol/L, **OR** Venous plasma glucose in a 2h sample (2hPG) of an oral glucose tolerance test (OGTT) ≥11.1 mmol/L A confirmatory test must be done on another day in all cases in the absence of unequivocal hyperglycaemia accompanied by acute metabolic decompensation Note: There is a change in FPG from 7.8 mmol/L in 1992 to 7.0 mmol/L in 1998 • Will result in more cases of DM being detected due to lower threshold • May affect disease prognosis as cases are identified earlier in disease process At the same time, there was a movement away from the use of the OGTT
2003[3]	FPG ≥7.0 mmol/L, **OR** Casual PG ≥11.1 mmol/L + symptoms of diabetes (e.g., polyuria, polydipsia, unexplained weight loss), **OR** 2hPG in 75g OGTT ≥11.1 mmol/L A confirmatory laboratory glucose test (FPG, causal PG, or 2hPG in a 75g OGTT) must be done in all cases on another day in the absence of unequivocal hyperglycaemia accompanied by acute metabolic decompensation Note: the term "prediabetes" was officially introduced in the 2003 CPGs
2008[4]	FPG ≥7.0 mmol/L, **OR** Casual PG ≥11.1 mmol/L + symptoms of diabetes (e.g., polyuria, polydipsia, unexplained weight loss), **OR** 2hPG in 75g OGTT ≥11.1 mmol/L A confirmatory laboratory glucose test (FPG, causal PG, or 2hPG in a 75g OGTT) must be done in all cases on another day in the absence of unequivocal hyperglycaemia accompanied by acute metabolic decompensation. However, in individuals in whom type 1 diabetes is a possibility (younger individuals and lean, older individuals), to avoid rapid deterioration, confirmatory testing should not delay initiation of treatment.

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APPENDIX B

DIABETES CARE PROGRAM OF NOVA SCOTIA: STANDARDIZED PHYSICIAN REFERRAL FORM

PHYSICIAN REFERRAL FORM
DIABETES CENTRE (DC)

[PLEASE PRINT]

Please complete the following information. It will serve as a referral to the DC as well as registry data for the Diabetes Care Program of Nova Scotia (DCPNS). Back page of form provides definitions, diagnostic criteria, and target values.

Name: _____
            last   first   initial

Address: _____
            street

_____
city/town   postal code

Health Card No.

Sex: ❑ M   ❑ F   D.O.B.: _____
                    dd   mm   yy

Phone (h) _____ (w) _____

Parent/Guardian: _____

Date of diagnosis: _____
              dd   mm   yy

Date referred: _____
              dd   mm   yy

Patient informed of referral? ❑ Y   ❑ N

DC USE ONLY

Date of DC appt: _____
              dd   mm   yy

Type of referral: ❑ ND   ❑ NND   ❑ NNDR

Previous diabetes education: ❑ Y   ❑ N   When/Where? _____

TYPE OF DIABETES (See back for definitions)

❑ Type 1   ❑ Type 2

❑ Impaired glucose tolerance (IGT) - Isolated

❑ Impaired fasting glucose (IFG) - Isolated

❑ IFG + IGT

❑ Other _____

If **pregnant** check below:

❑ Type 1   ❑ Type 2   ❑ GDM

❑ IGT of pregnancy   EDC _____

PRESENT TREATMENT

❑ Diet only

❑ Oral antihyperglycemic agent (OAA) + diet

❑ Insulin + diet

❑ Insulin + OAA + diet

MEDICAL PROBLEMS   ❑ NONE

❑ Thyroid

❑ Hypertension (>130/80)

❑ Dyslipidemia

❑ Cardiovascular disease (CVD)

❑ Smokes

❑ Alcoholism

❑ Overweight (BMI >25)

❑ Exercise restrictions _____

❑ Other _____

Microangiopathy

❑ Retinopathy

❑ Nephropathy

Miscellaneous

❑ Foot problems

❑ Neuropathy

FAMILY HISTORY (parents/sibs/children only)

Diabetes	❑ Y	❑ N
Cardiovascular disease	❑ Y	❑ N
Hypertension	❑ Y	❑ N
Obesity	❑ Y	❑ N

LABORATORY DATA
Please complete the following section to prevent duplication of testing. If not completed, the DC may repeat these tests to complete a comprehensive assessment. Report in SI units.

❑ **See attached copies**

MEDICATIONS (diabetes-related and other)   ❑ None
[name/dose/frequency]

❑ patient told to bring medications to DC

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Basis of Diagnosis

❑ **Symptomatic and Venous Plasma Glucose**

Date: _____

fasting: _____

casual: _____

Date: _____

fasting: _____

casual: _____

75g OGTT

Date: _____

fasting: _____

2-hour: _____

GESTATIONAL ONLY

50g Oral Glucose Challenge

Date: _____

1-hour: _____

(Please circle)

75g or 100g OGTT

Date: _____

ac: _____

1-hour: _____

2-hour: _____

3-hour: _____

Baseline Data

Date

Recent A1C: _____ _____

Recent BG: _____ _____
❑ Casual   ❑ Fasting

Check (√) test if completed in the past month.

❑ A1C   ❑ TG   ❑ T-Chol

❑ HDL-C   ❑ LDL-C

Check (√) test if completed in the past 3 months.

❑ Creat   ❑ TSH   ❑ Liver Function

❑ Proteinuria

❑ Other _____

PROBLEMS THAT MAY AFFECT LEARNING:
❑ physically challenged   ❑ mentally challenged   ❑ social situation
❑ attitude toward DM   ❑ financial   ❑ literacy
❑ drug use   ❑ emotional

MAY REQUIRE REFERRAL TO:
❑ foot care clinic   ❑ Home Care/VON   ❑ mental health
❑ diabetes specialist   ❑ ophthalmologist   ❑ other _____
❑ perinatologist   ❑ obstetrician

COMMENTS/SPECIAL INSTRUCTIONS:

❑ Transferred from (Name of DC): _____

Referring physician: _____
❑ Check if family MD same as referring.

print name   phone   signature

WHITE AND YELLOW COPIES--DIABETES CENTRE   PINK COPY--PHYSICIAN
Endorsed by the Medical Society of Nova Scotia

DCPNS Revised
March 2006

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Definitions:

Type 1 DM: Absolute deficiency of insulin secretion as a result of pancreatic β–cell destruction; prone to ketoacidosis.
Management: Insulin and nutrition therapy. Usual onset is under age 35 years.

Type 2 DM: Resistance to insulin and/or inadequate compensatory insulin secretory response. Includes LADA (latent autoimmune diabetes in adults).
Management: Nutrition therapy only; oral antihyperglycemic agents; insulin. Usual onset is over age 35 years.

Gestational Diabetes (GDM): Any degree of glucose intolerance with first onset in pregnancy.

Impaired Glucose Tolerance (IGT) &
Impaired Fasting Glucose (IFG): Prediabetes terms-- intermediates between normal glucose homeostasis and diabetes. These are risk factors for future diabetes and cardiovascular disease (CVD) and are not diagnostic of diabetes.
Management: Nutrition therapy only; lifestyle modifications--healthy eating, smoking cessation, and physical activity; consider pharmacotherapy in IGT (biguanide or alpha-glucosidase inhibitor).

Metabolic Syndrome: Significant risk for developing diabetes and CVD. Three or more of the following risk determinants are present: fasting plasma glucose (FPG) ≥ 6.1 mmol/L; BP ≥ 130/85 mmHg; TG ≥ 1.7 mmol/L; abnormal HDL-C (men < 1.0 mmol/L; women < 1.3 mmol/L); elevated waist circumference (men > 102 cm; women > 88 cm).

Diagnostic Criteria for DM in the Nonpregnant Adult:

1. A FPG ≥ 7.0 mmol/L. Fasting is defined as no caloric intake for at least 8 hours.
   OR
2. Casual plasma glucose (PG) value ≥ 11.1 mmol/L plus symptoms of diabetes. Casual is defined as any time of the day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.
   OR
3. The PG value in the 2-hr sample of the 75g OGTT is ≥ 11.1 mmol/L.

In the absence of unequivocal hyperglycemia accompanied by acute metabolic decompensation, a confirmatory test is required on another day.

Testing with a 2-hr PG in a 75g OGTT should be considered when FPG is 5.7 – 6.9 mmol/L to determine the presence of IGT.

Prediabetes - Impaired Fasting Glucose (IFG) & Impaired Glucose Tolerance (IGT):

* IFG is defined as: FPG of 6.1 – 6.9 mmol/L.
* IGT is defined as: FPG of < 6.1 mmol/L and a 2-hr (post 75g glucose load) PG of 7.8 mmol/L - 11.0 mmol/L.
  Interventions: Lifestyle modifications; increased frequency of rescreening.

Pregnant Population - All should be screened between 24 and 28 weeks (closer to 24):

1. Screen at 24 to 28 weeks gestation with a 50g oral glucose challenge (1st trimester in high-risk patients). PG is drawn at 1-hr pc.
   If the 1-hr PG is: • ≥ 7.8 mmol/L and ≤ 10.2 mmol/L, a 75g OGTT is recommended.
   • ≥ 10.3 mmol/L, GDM is present and the 75g OGTT is not necessary and contraindicated.

   Following an abnormal screen (7.8 – 10.2 mmol/L), challenge with a 2-hr 75g OGTT. (Other accepted methods such as the 100g OGTT may be used.) Proper preparation is needed for the OGTT.
   PG is drawn fasting, at 1-hr and at 2-hrs pc for the 75g.
   * Diagnostic for **GDM** following a 75g OGTT (two or more values are equal to or exceed the following):
     • FPG: 5.3 mmol/L   • 1-hr: 10.6 mmol/L   • 2-hr: 8.9 mmol/L

   * Diagnostic for **IGT of Pregnancy** (a single value is equal to or exceeds the above). Nutrition therapy is required.

Recommended Targets for Diabetes Control:

Glycated Hemoglobin (A1C): Measure approximately every 3 months.
* ≤ 7.0%. If it can be safely achieved, lowering toward normal (≤ 6.0%) should be considered.

Blood glucose: Optimal glucose control in non-pregnant adults and children over age 12 years:
* Fasting or preprandial PG: 4-7 mmol/L   • 2-hr PG: 5-10 mmol/L

Lipids: Measure fasting at diagnosis and repeat every 1 to 3 years as clinically indicated.
* Ratio TC:HDL-C: < 4   • LDL-C: < 2.5 mmol/L (under review)
* Triglycerides (TG):   < 1.5 mmol/L   • apo B (optional):   < 0.9 g/L (high-risk); < 1.05 g/L (moderate-risk)

Blood pressure (BP): Measure at diagnosis and every visit thereafter.
* ≤ 130/80 mmHg.

Recommendations:
* Diabetes self-management education. Initial and ongoing.
* Routine foot and eye examinations. Annual foot examination; eye examination through dilated pupils every 1 to 2 years.
* Routine self-monitoring of blood glucose (SMBG). Encourage interpretation and action. Individualize frequency of testing.
* Annual influenza vaccine. Consider immunization against pneumococcus.
* ASA treatment: 80-325 mg unless otherwise indicated.
* Screening for and intervention aimed at adjustment problems, depression, anxiety, and/or eating disorders.

Lifestyle modifications:
* Smoking prevention/cessation   • Healthy eating   • Weight management (BMI < 25)
* Active living/physical activity   • Waist circumference: men < 102 cm; women < 88 cm

Reference:
Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Can J Diabetes.* 2003;27(suppl 2):S1-S152. Website: http://www.diabetes.ca/cpg2003/

Appendix C

Diabetes Care Program of Nova Scotia: Standardized Patient Flow Sheet

FLOW SHEET
DIABETES CENTRE (DC)

Complete on each visit. Check box or record information as appropriate.

Date of diagnosis: _____ d _____ m _____ y

Type of diabetes: ☐ Type 1 ☐ Type 2 ☐ IGT ☐ IFG ☐ IGT & IFG

Acceptable wt. range (BMI 20-25): _____

Ht: _____ Htm²: _____ Goal Wt: _____ WC: _____

Unit No.
Name
Address
Sex
HC No.
Phone:

D.O.B.

Physician: _____

(H) _____ (W) _____

TREATMENT

LAB DATA

BLOOD GLUCOSE

DATE d/m/y (a)	C/G C/G T/I (a)	N √	D √	O √	Kg/ lbs (Circle) (b)	BP	Med	FT-A (c)	Fasting 2hr	Q A (e)	A1C	TC HDL	Ratio TC:HDL	LDL	TG	Med	Creat	CrCl	TSH	Prot/ Micro (g)	INSULIN/OAA (Type, Dosage, Time, Frequency)	Nutrition Therapy*		Exercise**

Allergies: ☐ Y ☐ N

(a) Seen at the lab only. Not a DC visit.
(b) Record weight change, BMI, or waist circumference, if applicable.
(c) BP med. Check Yes (Y), No (N), or change from previous visit(s). *See Med. Sheet.*
(d) Record capillary on top; lab on bottom.
(e) Local use.
(f) Lipid med. Check Yes (Y), No (N), or change from previous visit(s). *See Med. Sheet.*
(g) Record proteinuria on top; microalbuminuria (ACR) on bottom.
(h) Check if changed from previous visit.

*NUTRITION THERAPY (indicate type of meal plan provided; e.g., 1600 cals, CHO counting, ↓ Na, etc.) In the adjacent column, indicate adherence (Ad) to recommendation by circling appropriate # based on the categories noted below.
1. Follows as recommended.
2. Follows ≥ 4 days/week.
3. Unable/unwilling to follow.
4. Revised.

**EXERCISE (circle appropriate # based on categories below and write type of exercise in the adjacent column):
1. Consistent moderate exercise (≥ 30 min/day, ≥ 5 times/wk)
2. Regular but less than recommended.
3. Irregular and/or extreme variation in intensity.
4. Able but no attempt to exercise.
5. Unable due to medical conditions.

Nutrition Therapy* Ad: 1 2 3 4
Exercise** Circle: 1 2 3 4 5

TDD = _____ : _____   _____ u/Kg

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FLOW SHEET KEY

WC	Waist circumference
LOPD	Lab Outpatients only. No Diabetes Centre (DC) visit.
N √	Seen by nurse.
D √	Seen by dietitian.
O √	Seen by other discipline; e.g., MD, Social Worker, etc.
BP	Blood pressure
Med	Medication
FT-A	Foot Assessment - Indicate Risk (H-high, assess q 3-4 months; M-moderate, assess q 6 months; L-low, assess annually); or FC-foot clinic assessment outside DC (indicate date).

BLOOD GLUCOSE & LAB DATA

QA	Check (√) if lab to meter comparison completed.
A1C	Glycated Hemoglobin
TC:HDL	Ratio total cholesterol:High Density Lipoprotein-Cholesterol (TC divided by HDL-C)
LDL	Low Density Lipoprotein
TG	Triglycerides
Creat	Creatinine
CrCl	Creatinine clearance estimate as calculated by the Cockcroft-Gault Formula*
TSH	Thyroid function
Prot/Micro	Proteinuria/Microalbuminuria (ACR)
OAA	Oral Antihyperglycemic Agent

TREATMENT

TDD	Total daily dose (insulin)
u/Kg	Units per kilogram (TDD divided by weight in kg)

SELF CARE PRACTICES

M	Check (√) if using meter to test blood glucose.
AT	Check (√) if appropriate technique.
K	Check (√) if appropriate ketone testing; note n/a if not applicable.
Hypo	Hypoglycemia episodes (On top, indicate freq - times per week/On bottom, check (√) if appropriate treatment).
ID	Diabetes identification. Check Yes (Y) or No (N) if wearing ID. Check ▲ if subsequent changes; note change.
SM	Smokes - Check Yes (Y), No (N), or Quit (Q). Check (√) if subsequent changes; note change.
P	Check (√) to see progress notes.
R	Check (√) to indicate referral made elsewhere by DC staff - note in progress notes.
Initials	Health professionals' initials (room for 2).

*Calculation of creatinine clearance in adults using the Cockcroft-Gault Formula:

Creatinine clearance (mL/min) = (140-age in years) x actual weight (kg) / serum creatinine (μmol/L)   Multiply the result by 1.2 for men

Print Name	Signature	Initials

SELF-CARE PRACTICES

SMBG						HEALTH CARE BEHAVIOURS						
Freq Circle (i)	Use Circle (j)	A T	Comments (record recommendation)	K	Hypo Freq/ Appro. Tx	ID	Sm	Annual Flu Shot	Eye (Last date)	Dental	P (√)	R (√)	Initials (√) (e)
M □	1 2 3 4	1 2 3 4				Y □ N □	Y □ N □ Q □						
M □	1 2 3 4	1 2 3 4				▲ □	▲ □						
M □	1 2 3 4	1 2 3 4				▲ □	▲ □						
M □	1 2 3 4	1 2 3 4				▲ □	▲ □						
M □	1 2 3 4	1 2 3 4				▲ □	▲ □						
M □	1 2 3 4	1 2 3 4				▲ □	▲ □						
M □	1 2 3 4	1 2 3 4				▲ □	▲ □						

(i) Frequency:
1) Regular; as recommended.
2) Regular but less than recommended.
3) Only when feeling poorly.
4) Does not test.

(j) Use:
1) Uses results to modify treatment (diet, exercise, meds).
2) Understands results; does not adjust treatment.
3) Incorrect interpretation; inappropriate modification.
4) Does not use test results.

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