An assessment of risk factors for diabetic retinopathy in the Cree population of James Bay

by

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ABSTRACT

Diabetic retinopathy is the leading cause of blindness in working-aged North Americans. Native North Americans have an elevated prevalence of diabetes, making diabetic retinopathy an even more important health issue for this group.

This project evaluates risk factors for diabetic retinopathy in the Cree population of James Bay, Ontario using a retrospective cohort design with individuals previously diagnosed with diabetes. Hypertension, body-mass index, serum lipid levels, renal function status, and hemoglobin A1C were the main exposures of interest. Relative risks for the association of these variables with retinopathy were determined through a modified Cox's proportional hazards model.

The prevalence of diabetes in the James Bay Cree population was 5.5% (95% CI 4.9% to 6.1%). Thirty-four percent of all people with diabetes were found to have some evidence of diabetic retinopathy. Significant univariate risks for the development of retinopathy included duration of diabetes, body-mass index, hemoglobin A1C, fasting blood glucose, insulin treatment, and serum cholesterol levels.

In multivariate analysis, predictors of diabetic retinopathy included body-mass index and insulin treatment. An increase in body-mass index reduced the risk of diabetic retinopathy (Relative Risk [RR] 0.64 per five kg/m^2, 95% Confidence Interval [CI] 0.04 to 1.00). Insulin therapy was associated with an increased risk of retinopathy when compared to individuals on dietary therapy alone (Relative Risk [RR] 4.71, 95% Confidence Interval [CI] 1.16 to 19.16). For individuals with serum cholesterol levels above the average for the Cree diabetic population, 5.2 mmol/L, the risk of retinopathy was increased (Relative Risk [RR] 2.38, 95% Confidence Interval [CI] 0.98 to 5.79).

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LIST OF ABBREVIATIONS

BDR - Background Diabetic Retinopathy

BMI - Body-mass index

BUN - Blood urea nitrogen

CI - Confidence Interval

CNIB - Canadian National Institute for the Blind

CSME - Clinically Significant Macular Edema

EKG - Electrocardiogram

FBG - Fasting blood glucose

HDL - Serum high density lipoprotein

LDL - Serum low density lipoprotein

MI - Myocardial Infarction

PDR - Proliferative Diabetic Retinopathy

RR - Relative Risk

WESDR - The Wisconsin Epidemiologic Study of Diabetic Retinopathy

WHO - World Health Organization

X^2 - Chi-square

1.0 INTRODUCTION

1.1 BACKGROUND

Diabetes is a significant health issue for Canadians. At present, 1.5 million Canadians have been diagnosed with diabetes and an estimated 750,000 are still undiagnosed.[1,2] Native Canadians suffer from a significantly higher prevalence of diabetes than the general population.[3,4,5,6]

Diabetic retinopathy is a major complication of diabetes and can be found in as many as one-third of diabetics.[7] Canadian National Institute for the Blind (CNIB) figures indicate that diabetic retinopathy is the most common cause of blindness in working-aged individuals in North America.[8] Moreover, individuals with diabetes are 25 times more likely to become blind than persons in the general population.[9] As with diabetes, the prevalence of diabetic retinopathy is also elevated in native communities.[10,11]

There are two main forms of diabetic retinopathy that can lead to vision loss. The first type, neovascularization of the retina, results from a relative oxygen debt within the retina. Vasogenic factors are produced that trigger the growth of abnormal new vessels on the surface of the retina and into the vitreous. These abnormal new vessels are weak and prone to hemorrhaging; they also are subject to tractional forces exerted by the vitreous that can lead to retinal detachment and blindness.

The second type of diabetic retinopathy is macular edema. Chronic diabetes can damage the retinal blood vessels (microvasculature), allowing lipid and other serous blood constituents to extravasate into the surrounding retina. Accumulation of this fluid at or near the macula, the area of central vision, can lead to permanent loss of fine vision.

Asymptomatic diabetic retinopathy is prevalent and has a long latent period that precedes vision loss.[12,13] Fortunately, screening for retinopathy is non-invasive, cost-effective, and highly sensitive and specific.[14,15,16,17,18,19] Once detected, diabetic retinopathy is amenable to laser photocoagulation therapy, which has been shown to reduce markedly the risk of severe vision loss from neovascularization and macular edema.[20,21] For these reasons, screening for diabetic retinopathy is an important component of the ongoing care of diabetics.

In general, eye examinations for people with diabetes are arranged through referrals from family physicians or endocrinologists to ophthalmologists or retina specialists. Patients with diabetes should undergo screening for retinopathy on a yearly basis, [22] but unfortunately many do not follow-up on this recommendation. Up to 50% of Americans with diabetes do not have annual dilated eye examinations and 46% of those requiring laser treatment have not received this care.[23,24] In Canada, diabetics may rarely receive even biennial screening, as demonstrated in a study of Nova Scotians.[25] For regions where the prevalence of diabetes is high and access to specialty care is limited, such as in Canada's native communities, special screening arrangements are essential.

1.2 PRESENT STUDY

The importance of this research into risk factors for the development of diabetic retinopathy in the Cree of the James Bay region lies in the uniqueness and completeness of the population under study. To date, there is no published research evaluating contributing factors for the development of diabetic retinopathy in a Canadian native community. In fact, there is no research evaluating risks for diabetic retinopathy in any native community north

of South Dakota. Moreover, the absence of complete cohort data in the existing studies evaluating retinopathy in American Native populations has not allowed for the determination of relative risks for the development of this complication.[26,27]

This research project is based on a screening program for diabetic retinopathy begun by the Moose Factory Hospital Board in 1993. In addition to diabetic retinal examinations, the screening program was also intended to provide specialized retinal care for the diabetic Cree population of James Bay, Ontario. Data from the past four years of retinal care in Moose Factory and Moosonee was collected for the purpose of this project.

Using a retrospective cohort design, risk factors for diabetic retinopathy were examined in the cohort with diabetes from Moose Factory and Moosonee. Outpatient and inpatient chart data were available for this complete cohort allowing the calculation of relative risks for a variety of covariates. Suspected risk factors for diabetic retinopathy included the following: duration of diabetes, therapeutic regimen, body-mass index (BMI), hemoglobin A1C, fasting blood glucose, serum lipid levels, renal function status, hypertension and evidence of previous vascular disease.

The following section of this paper describes the current state of diabetes in Canada as well as known risk factors for diabetic retinopathy. Section three offers a brief overview of the population being studied. Section four presents the objectives of this research project and addresses issues of methodology and study design. Results are presented in section five with a discussion of these outcomes in section six. The discussion also presents recommendations that should be considered in future research into chronic diseases in native populations.

2.0 BACKGROUND

2.1 DIABETES IN THE CREE

The overall prevalence of self-reported diabetes in Canadian adults (age 18-74 years) was approximately 5.1% in the Canadian Health Survey,[1] but the percentage is sometimes higher in specific populations.[5] Some of the highest rates occur in Canadian native populations. For southern Canadian native populations, the prevalence of diabetes is significantly higher than most other Canadian populations.[6] Studies that deal specifically with the Cree population of Canada have focused on the Quebec Cree. These studies have found the age-standardized prevalence of diabetes to be approximately 7%.[28,29,30] This higher number may be indicative of recent, accelerated changes in lifestyle and diet that have been imposed upon North American native communities over the past century.[31]

2.2 DIABETIC RETINOPATHY

Diabetic retinopathy develops as a consequence of damage to the microvascular integrity of retinal blood vessels. The two processes believed most responsible are the thickening of the microvascular basement membrane and the loss of intramural pericytes (vascular supportive cells).[32] Both of these effects likely combine to disrupt the capillaries' permeability and structural integrity. The result is diabetic retinopathy, characterized by the following clinical findings: microaneurysm formation, dot/blot hemorrhages, nerve fibre layer hemorrhages, cotton-wool spots, macular edema, and retinal neovascularization. Of these, macular edema and retinal neovascularization are most likely to result in visual

impairment. Vision can also be lost as a consequence of macular ischemia--essentially a stroke involving the area of central vision. Macular ischemia was not considered in this study because it cannot be diagnosed clinically. Its diagnosis requires fluorescein angiography which, for logistical reasons, is not used to screen for diabetic retinopathy.

2.3 RISK FACTORS FOR DIABETIC RETINOPATHY

Much of our current understanding of the epidemiology of diabetic retinopathy has come from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR). This carefully constructed prospective cohort study has provided incidence rates and risk factor information for proliferative diabetic retinopathy, macular edema, and background retinopathy for a primarily rural/suburban caucasian population.[33,34,35,36,37,38] The WESDR's assessment of the risks for the development of diabetic retinopathy were analyzed for two populations with diabetes, those diagnosed before age 30 and those diagnosed after. Multivariate analyses were employed to determine the relative effects of individual risks on retinopathy for all the WESDR studies.

In the WESDR's population with older onset diabetes, a Cox's proportional hazards analysis demonstrated that duration of diabetes, higher glycosylated hemoglogin, and higher systolic blood pressure were all associated with severity of retinopathy. The WESDR also demonstrated that risk factors for proliferative retinopathy in older individuals with diabetes included poorly controlled hyperglycemia, duration of diabetes, hypertension, and severity of background retinopathy. Risks for the development of macular edema for older onset diabetics were increased glycosylated hemoglobin, female sex, duration of diabetes, severity of background retinopathy, and elevated diastolic blood pressure. The risks for retinopathy in the older cohort of Wisconsin subjects is more

relevant for this study because diabetes in North American Native populations is almost exclusively adult onset, also known as type 2.

Other systemic factors have been examined in the setting of diabetic retinopathy in caucasian populations; however, the data supporting a link between these risks and retinopathy are not clearly defined at present. Such potential factors include serum lipid levels, renal status, BMI, and fasting blood glucose levels.

The major risk factors for the development of diabetic retinopathy are reviewed in more detail below.

2.3.1 Duration of Diabetes

Of the variables that are predictive of retinopathy, one of the strongest is duration of diabetes. Many studies have confirmed the association between duration of diabetes and retinopathy.[33,39,39] The expected pathophysiologic mechanism for this effect is not completely understood at present; however, it is believed to be related to the inability of aldose reductase to efficiently metabolize glucose. The effect of duration of diabetes on retinopathy seems to be related to long-term changes in the sorbitol pathway that result in chronically elevated levels of sorbitol. This, in turn, appears to have a cumulative, detrimental effect on the body's microvasculature.

2.3.2 Hypertension

Considerable study has focused on the role that primary hypertension plays in the development of diabetic retinopathy.[40,41] Elevated systolic and diastolic blood pressures have been shown to increase the risk of retinopathy. The mechanism for this association is believed to be related to the harmful effect of elevated pressure on the systemic vasculature and microvasculature.

The relationship between hypertension and diabetic retinopathy has been demonstrated for primary hypertension and is thought to be independent of hypertension secondary to renal failure from diabetic nephropathy.

Diabetic nephropathy and secondary hypertension are related to the overall progression of diabetic vasculopathy. As such, the development of secondary hypertension is a co-morbid process that typically progresses in a temporally parallel manner to retinopathy. Once secondary hypertension develops, it could be expected to accelerate the progression of retinopathy; however, its role in the development of retinopathy is not known.

2.3.3 Control of Blood Glucose

Strong evidence has been put forward to demonstrate a relationship between strict control of serum blood glucose and a delay in progression and development of diabetic retinopathy.[42] The Diabetes Control and Complication Trial randomized diabetics to 'strict control' or 'standard control' groups and followed these individuals for the development of late diabetic complications. After only two years of follow-up, significantly less progression of retinopathy and less development of retinopathy were noted in those participants who were under 'strict' blood sugar control.

Probably the best single measure of long-term blood sugar control is the serum hemoglobin A1C level. As demonstrated in the WESDR, higher levels of this variable were significantly associated with progression to proliferative retinopathy and to macular edema.

2.4 RETINOPATHY RISKS IN NATIVE POPULATIONS

As indicated earlier, there is a higher prevalence of diabetes in North American native compared to non-native populations. Among native populations, too, the figures differ greatly. For example, the Oklahoma Plains Indians reportedly have a 33% prevalence of diabetes for those over 30 years of age.[31] That number rises markedly to 48.9% in Arizona Pima Indians who are >35 years of age--the highest prevalence of diabetes in the world.[43] The 7% prevalence of the James Bay Cree, in contrast, is much closer to that of Canadian caucasian populations (5.1%).[1]

Whereas diabetes prevalence studies have demonstrated significant differences between caucasian and native populations and among various native populations, there is relatively little data that would allow comparison of incidence or prevalence rates for diabetic retinopathy in these groups.

While there is a lack of information on diabetic retinopathy in general, the incidence rates of proliferative retinopathy appear roughly comparable between the Pima Indians and the WESDR populations.[44,45] Nonetheless, the different genetic heritages and physical environments of these populations would be expected to modify the physiologic processes responsible for diabetic retinopathy. Risk factors for the development of retinopathy would also be expected to have different inter-relationships and magnitudes of effect in different populations. These possible risk factor differences have been the focus of recent investigations concerning the study of diabetic retinopathy in native American populations.[26,27,46,47]

To date, the examination of retinopathy risks for North American Native

populations has been carried out in only three populations: the Gila River Indians of Arizona, the Plains Indians of Oklahoma, and the South Dakota Sioux.

2.4.1 The Pima and Papago Indians

The Pima and Papago Indians of Arizona have been closely followed for diabetes and its complications since 1965. The first large study of retinopathy in the Pima Indians was published in 1976 by Dorf.[46] It demonstrated that retinopathy was more prevalent in natives with elevated two-hour plasma glucose levels and those with a longer duration of diabetes. While the absence of appropriate multivariate statistical analyses did not allow for robust conclusions to be drawn, Dorf's analysis nonetheless paved the way for further, more careful studies of the Arizona native population.

One such study was Nelson's, which examined risks for proliferative retinopathy in the same Pima population that Dorf followed.[44] Age, duration of diabetes, hypertension, proteinuria, renal insufficiency, absence of the Achilles tendon reflex, elevated total serum cholesterol, and treatment with insulin were all associated with proliferative disease. The paper provided a more methodologically rigorous examination of risk factors; however, its scope was limited to proliferative retinopathy.

There are only four papers in the literature that provide an in-depth, controlled, multivariate analysis of risks for all forms of diabetic retinopathy in a North American native population. Nagi's recent paper in Diabetic Medicine is one of these.[47] It examined risk factors for diabetic retinopathy using a 45 degree fundus camera to grade retinopathy. (Using a camera to screen for diabetic retinopathy has been well validated, demonstrating sensitivity and specificity rates comparable to examinations performed by ophthalmologists and retina specialists.[48]) The paper looked at two outcomes that had not before been assessed in the Pima Indians: retinopathy at the time of diagnosis of diabetes, and non-

proliferative diabetic retinopathy. Lower BMI and elevated blood pressure were predictors of retinopathy diagnosed simultaneously with diabetes; degree of glycemia was not associated. For non-proliferative retinopathy, duration of diabetes, mean blood pressure, fasting blood sugar, insulin therapy, and albuminuria were all associated.

This latter set of results is significant with respect to this thesis because non-proliferative retinopathy accounts for the vast majority of retinopathy seen; it is also the primary form of retinopathy encountered in diabetics examined in Moose Factory and Moosonee.

2.4.2 The Oklahoma Plains Indians

Two epidemiologic studies on the same population of Oklahoma Indians have specifically evaluated risks for diabetic retinopathy.[26,27] These studies, conducted twelve years apart, employed multivariate logistic regression and demonstrated that fasting plasma glucose, duration of diabetes, and therapeutic regimen were all independent predictors of retinopathy.

2.4.3 The South Dakota Sioux

A recent paper evaluated risk factors for diabetic retinopathy in the South Dakota Sioux as part of the Strong Heart Study.[49] Risk factors for retinopathy were studied in 417 individuals who had retinal fundus photos taken for grading the severity of retinopathy, the outcome variable. Significant univariate associations were found, including fasting blood glucose, systolic blood pressure, urinary albumin-to-creatinine ratio, renal dialysis, and duration of diabetes. Extensive multivariate analyses were not presented in this study.

2.4.4 The James Bay Cree

There are no papers that have looked at risks specifically for diabetic retinopathy in northern North American or Canadian native populations. However, Brassard's 1995 study, which examined risk factors for diabetic microangiopathy (defined as retinopathy or nephropathy) in the Cree of Quebec,[50] found that risks for diabetic microvascular disease included duration of diabetes, triglyceride levels, and insulin therapy. Unfortunately, this study had a methodologically weak outcome determination and no examination of diabetic retinopathy risk factors independent of nephropathy. In addition, retinal specialists were not used to determine the presence or absence or retinopathy. Nonetheless, this study did raise the issue of lipid disorders as significant contributors to microangiopathy and thereby possibly to retinopathy in the Cree population.

2.4.5 Rationale

The Oklahoma, Pima, and Sioux Indians are the only North American native populations to have had risks for diabetic retinopathy examined. However, the findings in these populations cannot be assumed to apply to all native peoples. The heritage of First Nation Peoples is extremely varied, as are the environments in which they live--hence the varied diabetes prevalences found across native populations in North America. (See section 2.4) As a result, diabetes in Canadian native populations is likely a somewhat different disease from diabetes in natives of the southern United States. It follows that the aforementioned studies of diabetic retinopathy risk factors in North American natives cannot be assumed to apply to the cohort under consideration in this paper. At present, no studies exist that have looked at risk factors for diabetic retinopathy in a northern native population.

This thesis examines the specific risks for retinopathy in the Cree of James Bay,

Ontario. Of particular interest are risk factors for retinopathy that are potentially modifiable: hypertension, BMI, hemoglobin A1C, and serum lipid levels. If associations between certain risks and retinopathy are demonstrated, hypotheses can be generated that could guide protocols for further prospective cohort studies. Ultimately, there may be a role for the medical management of systemic medical parameters that could help delay or prevent the onset of retinopathy, and hence blindness, in the Cree population. More immediately, the identification of specific risk factors for diabetic retinopathy would aid in targeting diabetics at higher risk for screening efforts -- increasing the thoroughness of present screening programs.

3.0 DIABETIC RETINOPATHY IN JAMES BAY

3.1 POPULATION AND SETTING

The communities of western James Bay include Moose Factory, Moosonee, Attawapiskat, Kashechewan, Fort Albany, Peawanuk, and New Post. The combined population of these communities is approximately 11,000 and the inhabitants are predominantly Cree, one of several tribes that comprise the Algonquin peoples.[51,52] Moose Factory and Moosonee are the largest communities in the region and are the focus for this study. Located at the mouth of the Moose River, Moose Factory is on an island in the middle of the river and Moosonee is on the mainland. The inhabitants number 2,800 and 2,300 respectively and are almost all Cree. The populations of interest are very stable with little out or in migration.

Weeneebayko General Hospital in Moose Factory is the only hospital in the region. All health care for the population of Moose Factory is provided in the outpatient family medicine clinic at this hospital. Moosonee residents have a health clinic in their town and more intensive care is provided through the Weeneebayko General.

Travel to the communities of western James Bay is primarily by air. A rail line does reach Moosonee but there is no road into the region from the south. All these communities can be considered 'remote'; there is little contact from non-native populations and traditional hunting and gathering practices are still maintained.

3.2 PRESENT STATE OF DIABETIC CARE IN JAMES BAY

At present, screening for diabetic retinopathy in the Cree population of James Bay is carried out by ophthalmologists as part of a Mushkegowuk Band Council initiative. In

the last two years approximately 75% of individuals with diabetes in Moose Factory and Moosonee have been seen by the retina specialists of Queen's University, Kingston, during yearly visits. Prior to this, from 1993 to 1995, retinal screening was provided by a retinal specialist through the University of Western Ontario, London. Overall, since screening was initiated, some four-and-a-half years ago, approximately 82.5% of all known people with diabetes in Moose Factory and Moosonee have been screened.[53]

4.0 DESIGN AND METHODS

4.1 OBJECTIVES

The main objective of this thesis is to examine the risk factors for diabetic retinopathy in the Cree population of Moose Factory and Moosonee. The primary risk factors of interest are potentially modifiable ones including body-mass index, hemoglobin A1C, and serum lipid levels.

Secondary objectives include an assessment of effect modifiers on the development of diabetic retinopathy and a determination of diabetic prevalence in Moose Factory and Moosonee. Also, Poisson regression is compared to the modified Cox's proportional hazards model as a secondary component of the analysis.

4.2 DESIGN

This study employed a retrospective cohort design. All diabetics in Moose Factory and Moosonee comprised the cohort, which was identified from hospital outpatient records. Data from ophthalmic examinations were collected for all individuals with diabetes to identify the presence or absence of retinopathy. Information on past exposures was obtained from the patient charts for the five-year period beginning the first year after each individual's diagnosis of diabetes. The chart review was performed by two researchers using a standardized data collection sheet.

Those individuals identified with diabetic retinopathy, as diagnosed by the retinal screening program, were considered to have developed the outcome of interest. Non-diseased patients included all people with diabetes but without retinopathy who had previously been screened.

4.3 IDENTIFICATION OF THE COHORT

All charts for patients with diabetes from the Moose Factory and Moosonee outpatient clinics were retrospectively reviewed during two data-collection trips to the region. Data abstractors recorded all exposure information before recording retinopathy status from the charts.

The diagnosis of diabetes was determined primarily by fasting blood glucose studies taken during the course of routine medical care at the Moose Factory and Moosonee Community Medical Clinics. The attending physicians at the clinics used standard World Health Organization (WHO) criteria to determine the diagnosis of diabetes. Specifically, patients were diagnosed as having diabetes if fasting blood glucose levels were above 7.8 mmol/L or oral glucose tolerance test levels were > 11.1 mmol/L.[54] Diabetics with gestational diabetes or secondary diabetes were excluded, as were those who had not had an ocular assessment. Non-natives with diabetes were also excluded.

For this study, a distinction of type 1 vs. type 2 diabetes was not made. This decision was based on information from the first 1997 diabetic retinopathy screening session in Moose Factory that did not identify any type I diabetics. The low prevalence of type I diabetes in Moosonee and Moose Factory is corroborated by Brassard's study of diabetes in the Quebec Cree. In this latter population, the prevalence of type 1 diabetes was found to be <0.1%.[29]

4.4 OUTCOME ASSESSMENT

The diagnosis of diabetic retinopathy was made by one of three retinal specialists during the course of screening visits to Moose Factory where screening for diabetic

retinopathy has been carried out since 1993. Criteria for the diagnosis of retinopathy were a modification of those adopted in the WESDR.[38] Typically, one of four specific diagnostic sub-categories was assigned: no retinopathy - level 10, background retinopathy (BDR) - levels 21 to 51, macular edema (CSME), and proliferative diabetic retinopathy (PDR) - levels 60 to 80. Retinopathy levels were defined by the more seriously affected eye. All examinations included indirect ophthalmoscopy, and contact lens or slit-lamp indirect biomicroscopy.

The ophthalmic literature suggests that there is negligible inter-observer variability for the diagnosis of diabetic retinopathy made by retina specialists. The strength of this relationship may not apply to other health care providers.[55,56] Therefore, only examinations performed by the three participating retina specialists were considered acceptable for the determination of retinopathy status. Individuals who had been diagnosed with retinopathy prior to the organized screening visits or who have not been examined by the participating specialists were not included. This was done, firstly, to maximize diagnostic accuracy and, secondly, to decrease the possibility that poor vision could potentially confound exposures such as BMI and treatment status. (Poor vision from retinopathy could theoretically lead to a lifestyle that is more sedentary, affecting variables such as BMI and diabetic treatment status.)

For the purpose of this study, retinopathy was not broken down into its specific sub-groups. The presence or absence of retinopathy was the primary outcome of interest. For individuals with multiple ocular examinations, the first diagnosis of retinopathy was considered the 'defining eye exam'. For those without retinopathy, the most recent eye examination was considered the 'defining' eye exam. An assumption of the irreversibility

of retinopathy was made. The assumption of irreversibility did not pose a problem as retinopathy did not change status from 'present' to 'absent' in any of the patients who had multiple ocular assessments.

4.5 EXPOSURE ASSESSMENT

All known potential risk factors for the development of retinopathy that were available from the patients' charts were recorded during the data collection process. Outpatient clinic charts as well as inpatient records were reviewed for each individual. Measures for possible confounders and/or effect modifiers for diabetic retinopathy were also collected. For each subject, measures of each covariate were taken from examinations or tests performed prior to the diagnosis of retinopathy but after the diagnosis of diabetes.

All efforts were made to collect measures for blood tests and physical examination findings that were performed during the five-year period starting one-year following the diagnosis of diabetes. The use of this specific five-year time block was to create a degree of standardization for the risk factors under study. Data from studies and examinations performed during the first year of diabetes were excluded in an attempt to eliminate values from tests that were performed prior to the patient having achieved a degree of stability in her diabetic therapy and hence her general physical condition. Theoretically, patients with recently diagnosed diabetes would be more likely to be in a period of dietary and therapeutic flux for the first year following their diagnosis.

For subjects with multiple test results within the five-year window of interest, test values from studies performed at approximately year-two, post diagnosis, were preferentially recorded. Individuals without data for variables from within this 5 year range had values recorded for examinations nearest to this time period, but they were not included in the main analysis. This led to a reduction in the size of the cohort used for the primary

analyses because hemoglobin A1C and complete lipid studies were not available until 1987. As a result, many with longstanding diabetes were only included in the descriptive analyses, Section 5.1. A more limited cohort was examined for the univariate and multivariate analyses that are the focus of this paper--mostly individuals who had their diabetes diagnosed within the last 10 to 15 years. (The group with this data is referred to as the 'limited cohort'.)

Although it reduced the power of this analysis by decreasing the number of individuals included, limiting data acquisition to a specific period was expected to give a much more accurate representation of the effects of the independent variables for the development of diabetic retinopathy. To have simply recorded arbitrary lab or examination values from any point in a patient's disease history would have limited the likelihood that these tests were measuring comparable variable values. An alternate approach would have been to choose lab or examination data for a specific period preceding an individual's ophthalmic examination. However, the choice of data from such a period would potentially have made the values of the covariates simply reflect the duration of diabetes; differences in covariate measures might be more a result of changes due to a patient's duration of diabetes than inter-subject differences responsible for the development of retinopathy. In this case, the study's power would also be potentially reduced.

Using a single measure from the defined five-year time interval for each exposure does not ensure that each variable's recorded value represents a patient's long-term exposure status. However, the specific temporal criteria imposed upon the limited cohort is assumed to give a more standardized exposure assessment for the limited cohort--and does give a proxy representation of each subject's chronic exposure status.

In the analysis section of this paper, data will be presented comparing the features of the full cohort of people with diabetes to the restricted, time-limited cohort. The main analyses will be restricted to the 'limited cohort'.

4.6 SPECIFIC COVARIATE DEFINITIONS

The definition of factors of interest and how they were assessed is presented below. All efforts were made to collect variable data as continuous. Only where this was not possible, because of the nature of the variable or chart limitations, were dichotomous representations used for data collection.

4.6.1 Age

This variable was recorded as the age of the patient at the time of his or her defining ocular examination, except for the comparisons in Table 5.1.4. In this one situation, age was defined as of January 1, 1998.

4.6.2 Duration of Diabetes

Duration of diabetes was defined in two ways for different parts of this study. These two definitions are presented in sections 4.6.2 and 4.6.3.

For analyses that involved individuals who had not had eye examinations (results section 5.1), duration was calculated as 'years an individual had diabetes as of January 1, 1998'. The onset date of diabetes was taken from the patient chart from a lab value consistent with diabetes that was corroborated by a physician's note documenting the diagnosis of diabetes. Where physicians' notes did not document the onset of diabetes, this point in time was defined from the oldest lab value meeting the WHO criteria for diabetes. (As noted previously, there is little chance that patients living in Moose Factory or Moosonee could have had their diabetes diagnosed at other medical clinics or laboratories. The stability of the population and singularity of the medical facilities makes this unlikely.)

4.6.3 Duration of Diabetes at Ocular Examination

The definition of duration of diabetes for the main analyses (result sections 5.2 to 5.6) was 'the time in years from diagnosis of diabetes to ocular examination'. This definition afforded a more accurate representation of duration of diabetes because it took into account the fact that certain individuals had not been seen in the general or specialty clinics for months or years following their last ocular assessment. Duration was thus defined by the date when retinopathy was determined, eliminating the possibility that individuals without retinopathy could have developed this outcome since their last ocular assessment. Except for the initial comparison of those with and without eye examinations (Table 5.1.4), duration of diabetes uses this definition.

4.6.4 Treatment Regimen

Treatment status was recorded as diet only, oral hypoglycemic, or insulin. Data were recorded at the time of the diagnosis of diabetes and at each point that a change in treatment was noted on a patient's chart. The therapeutic category to which a patient was assigned was the treatment regimen the patient was on for the majority of the period for years one to six following the diagnosis of his or her diabetes. The choice of this definition was made to give a more accurate representation of the therapeutic status of a patient independent of duration of diabetes. Using the therapeutic regimen that a patient was on for the majority of his or her disease course would potentially correlate this variable more closely with duration of diabetes--assuming there is a progression from diet to oral therapy and possibly to insulin. (No individuals were on insulin and oral hypoglycemics simultaneously.)

4.6.5 Laboratory Studies

Data from all from blood studies were recorded for the one- to six-year post diagnosis period if tests were performed prior to ophthalmic assessment. All data was taken from studies performed in the lab at the Weeneebayko General Hospital using standardized techniques. Lab tests for patients from Moosonee were also performed at the Weeneebayko Hospital laboratory.

- Fasting blood glucose: Considered a short-term indicator of diabetic control, this test was performed on blood samples taken in the morning prior to any caloric intake.
- Hemoglobin A1C (Glycosylated hemoglobin): This variable provided an accurate indication of long-term blood sugar control, significantly different information than a fasting blood glucose level provides. Co-linearity would be expected between this variable and fasting blood sugar if a diabetic's blood sugar control was exceptionally good or poor since it would likely produce similarly low or high levels for both tests.
- Renal function tests - Blood urea nitrogen, serum creatinine: Renal damage is a co-morbid feature of diabetes and not necessarily a risk for retinopathy; however, limited renal function might predispose an individual to retinopathy through the reduced clearance of vasogenic factors or vascular toxins. Data were not included for this variable for individuals in whom renal failure that was not due to diabetes.
- Serum lipid levels: Serum triglycerides have been shown to correlate with diabetic retinopathy and nephropathy in the Cree population.[50] For this study, data were collected for serum cholesterol, low density lipoprotein, high density lipoprotein, and triglyceride levels.

4.6.6 Body-mass Index

Because the value of body-mass index could change considerably after the initiation of diabetic therapy, BMI was calculated from weight data taken during the five-year variable assessment period (years one to six post diagnosis). Height values were taken from any recorded height for individuals over 20. For those under 20 (youngest was 18), the most up-to-date height was recorded. BMI was calculated as the ratio of weight to the square of the height (kg/m^2).

Since visual disability can affect one's ability to maintain activity levels, BMI could have been elevated as a result of diabetic retinopathy that was associated with vision loss, confounding the relationship between BMI and retinopathy. However, because BMI values were taken from the first six years post diagnosis, this potential confounder was not an issue. (No subjects lost vision from diabetic retinopathy in both eyes during the first six years post diagnosis of diabetes.)

4.6.7 Hypertension and Blood Pressure

Hypertension was considered present if a patient was taking medications for control of blood pressure. Blood pressure measurements were also documented from the five-year variable assessment interval. Systolic and diastolic values were recorded for the nearest date to the rest of the laboratory values.

4.6.8 Smoking

Data on pack-years of smoking was not consistently available in the patient charts. As a result, smoking history was recorded as ever or never.

4.6.9 Macrovascular Complications of Diabetes

Macrovascular complications of diabetes included a history of stroke or myocardial infarction. Data on the occurrence of each of two potential co-morbidities were recorded as having taken place or not following the diagnosis of diabetes. The diagnosis of these conditions was based on a physician-completed problem sheet in the patients' charts. If this information was not recorded on the problem sheet, then progress notes, written orders, and electro-cardiogram (EKG) reports were examined.

A stroke was documented as having occurred if there was an indication of a cerebral vascular event with neurologic residua; transient ischemic attacks were not recorded as a 'stroke'. Myocardial infarction was considered positive if changes consistent with an myocardial infarction (MI) were found for creatinine kinase-MB, or a physician-reported EKG.

4.6.10 Unavailable Data

Certain variables were not readily available from the chart review. Specifically, family history of diabetes, alcohol consumption, and diet (traditional, western, other) were not possible to collect.

4.7 DATA EDITING

Examination of the actual data measures was carried out to determine if any out of range values were present for age, lab-tests, BMI, etc. Out of range values were rechecked on the data collection sheets and, where necessary, reassessed through follow-up contact with the hospital medical records department.

Missing data were also filled-in where possible with dictated ophthalmic patient

reports. (For all patients seen in 1996 and 1997, ocular assessment notes were dictated at the time of examination.)

4.8 POWER ASSESSMENT

For this study, a fixed geographic population was examined. It was estimated that there were approximately 300 people with diabetes in Moose Factory and Moosonee.[61] During the course of this study, 283 patients were identified from the patient records at the two outpatient clinics. Of these 283 patients, 241 had eye examinations, and of these 241, 157 had lab/examination data from years one to six following their diagnosis of diabetes. This latter group comprised the limited cohort. Assuming that 75% of the 157 had complete chart data, the power calculation was based on 118 individuals. The power of this study was calculated to determine whether the study population was adequate to demonstrate a significant difference between those with and without risk factors for the development of diabetic retinopathy.

Study power was calculated specifically for fasting blood glucose as a risk for diabetic retinopathy.[57] Fasting blood glucose was anticipated to be an exposure that would be representative of other factors being examined in the study. For the purpose of the power estimation, the risk estimate (1.5) and exposure prevalence (64%) for FBG were taken from published data on Oklahoma Indians.[26] The limited cohort was used to determine the total number of individuals available for study.

Nomenclature[58]:

p_0 = proportion of non-exposed who develop retinopathy

p_1 = proportion of exposed who develop retinopathy

p = weighted average of proportions

n = number of exposed individuals (elevated fasting blood sugar)

r = ratio of number unexposed to exposed

d* = difference between proportions p_1 and p_0

alpha = 0.05

Z_B = standard normal deviate, corresponding to an alpha of 0.05, for the distribution around d*.

$$Z_\beta = \sqrt{\frac{nr(d*)^2}{p(1-p)(r+1)}} - Z_{\alpha/2}$$

4.8.1 Fasting Blood Glucose

The power to detect a relative risk of 1.5 for the presence or absence of elevated blood glucose was 0.81. Elevated fasting blood glucose was defined as >7.8 mmol/L, 64% of subjects were exposed. (p_0 = 0.51, p_1 = 0.77, n = 75, r = 0.57)

4.9 ETHICS

4.9.1 Hospital Board, Community Consent, and Ethics Review

This study was considered an extension of the diabetic retinopathy screening program that was initiated by Dr. Tom Chang in 1993. However, prior to initiating the

present study, specific approval was received from the Weeneebayko General Hospital Board for proceeding with this specific research project. The Weeneebayko hospital board included two representatives from each Cree community that received medical (and ophthalmic) care through the Weeneebayko Hospital/Queen's University affiliation. All of these board members, the hospital CEO, and the chief medical officer supported the decision to approve this research into diabetic retinopathy.

This study protocol was also approved by the Queen's University Health Sciences Human Research Ethics Board.

4.9.2 Individual Confidentiality

Individuals were not identified during the course of this study, data analysis, or in the course of data presentation.

4.9.3 Research Results

Prior to the publication or public presentation of any results from this study, the research results were presented to the Weeneebayko General Hospital Board and the Muskego Tribal Council.

4.10 DATA ANALYSIS

This was a retrospective cohort study; therefore, calculated risk estimates represent the actual relative risk of retinopathy for individuals with a risk factor compared to those without the same risk factor. A proportional hazards, multiple regression model was used for this assessment to determine the adjusted contributions of specific risk factors for the development of retinopathy. This statistical technique allowed the calculation of risk ratios for the population under investigation. To examine the accuracy of results obtained using

the proportional hazards model, a Poisson regression model was also performed for comparison purposes.

4.10.1 Initial Variable Conceptualization

The following section describes the representation of covariates that was used for the initial descriptive data analysis and for the comparison of those who had retinal assessments and those who were not examined.

- Age - continuous variable (integer)
- Sex - dichotomous variable (female = 1)
- Duration of Diabetes - continuous variable (integer)
- Diabetes Diagnosis to Ocular Diagnosis - continuous variable (integer)
- Present Therapy - categorical (recorded as either: 'diet', 'oral', or 'insulin'; Diet controlled diabetes were considered the baseline for the dummy variable representations in the multivariate models.)
- Hemoglobin A1C - continuous variable (to three decimal places)
- Fasting Blood Glucose - continuous variable (to two decimal places)
- Serum Lipid Levels - all four variables were conceptualized as continuous (to two decimal places)
- Renal Function - both continuous variables (blood urea nitrogen to one decimal place; creatinine as an integer)
- BMI - continuous variable (to two decimal places)
- Hypertension - dichotomous variable (positive if taking medication for hypertension)
- Systolic and Diastolic Blood Pressure - both continuous variables measured in mmHg (integers)

- Smoking - dichotomous (ever/never)
- Macrovascular Disease: Stroke, Myocardial Infarction - considered together as a single dichotomous variable ('positive' if a history of one of these two disorders was found)

4.10.2 Descriptive Statistics

Descriptive statistics were calculated using the SPSS statistical program. Initial assessment involved examination of features of the sub-population of people with diabetes who had not had ophthalmic assessments. This was performed to determine if there were any strong demographic differences and, consequently, evidence of possible selection bias for those with or without eye examinations.

Following this, extensive summary statistics were calculated for the full cohort that had attended screening examinations and for the sub-set of people with examination data from years one to six post diagnosis of diabetes. A number of representative variables were compared for both the extended and for the limited cohort, the specific group with the more precise data collection period.

Complete summary statistics and graphical representations were then performed for the limited cohort, including histograms, medians, ranges, means, standard deviations, and quartiles.

4.10.3 Relationships Between Independent Variables

This data was presented to describe the relationships and strength of relationships between covariates for the main risk factors and effect modifiers of interest. Pearson's product moment correlation coefficients were used to compare continuous variables, and Student's t-tests were used to compare dichotomous with continuous variables. For treatment regimen, the only categorical variable, analysis of variance was used to compare

the means for categories of continuous varibles. Comparisons between dichotomous and dichotomous, or dichotomous and categorical variables were performed with the X^2-test using a continuity correction for two-by-two tables. In situations where duration of diabetes or serum triglyceride levels were considered, the appropriate non-parametric tests were used, namely, Spearman's rank-order test and the Mann-Whitney U test (results section 5.2.1).

Highly correlated variables, or variables with significant t-tests, ANOVA, or X^2-tests were considered correlated and potentially collinear. Correlations between variables were sought to give an indication of the strength of relationship between variables and the possible effect that that could have had upon the proportional hazards model. For example, if a variable showed a strong univariate association with retinopathy and lost its significance on multivariate testing, the correlation/association tests could provide an indication of the nature of the possible inter-variable relationships responsible for this change in significance.

4.10.4 Univariate Comparisons for Diabetic Retinopathy

Univariate comparisons were calculated for each independent variable with diabetic retinopathy. Continuous variables were compared using the Student t-test while categorical variables were analyzed with the X^2-test. In situations where dichotomous variables were compared using a 2x2 table, a continuity correction was used.

4.10.5 Variable Representation

All continuous variables were initially tested for fit individually in Cox's models using three different representations: continuous, dichotomous (values separated by the

mean) and quartiles. Final log-likelihood ratios and p-values were taken from the univariate models and compared.

The log-likelihood ratio statistic was used to determine which representation of each variable had the strongest association with retinopathy. P-values for each of the three models were compared and the representation that demonstrated the strongest association was used for the forward stepwise assessment that followed. Variables that were conceptualized in a continuous or dichotomous fashion increased the power of the analysis by preserving degrees of freedom in the multivariate model.

4.10.6 Proportional Hazards Model

A modified proportional hazards model was used for the purpose of examining the main variables of interest while controlling for the effects of other variables. Since accurate temporal data was not available regarding the onset of retinopathy for all patients, a true Cox's model could not be used. Instead, a modified proportional hazards model was used that assigned the same failure time to each individual. This use of the proportional hazards model allowed the determination of relative risks from the specific variable coefficients, a result that logistic regression would not have allowed.

Typically, logistic regression has been used to calculate odds ratios for independent variables when an outcome is dichotomous. Invariably, this approach has been applied in the setting of case-control studies. The resulting odds ratios approximate relative risks if the rare disease assumption holds.

In this study, a retrospective cohort design was used, allowing for the calculation of relative risks; however, because the rare disease assumption was not expected to hold--retinopathy is relatively common--a logistic regression approach to this analysis would not

have resulted in an appropriate estimation of the relative risk.[59] Similar approaches have been employed for the determination of relative risk in the setting of prospective binomial data.[60]

As noted above, the independent variables for the Cox's model included potential confounders and effect modifiers for diabetic retinopathy as well as risk factors that were potentially amenable to medical management or lifestyle alteration: BMI, hypertension, hemoglobin A1C, fasting blood glucose, renal function, smoking status, and serum lipid levels. The presence or absence of retinopathy was the dependent variable.

The EGRET statistical package was used to perform the multiple regression component of this analysis. Initially, all significant, transformed univariate terms were entered in a forward, stepwise approach to derive a parsimonious model. A liberal inclusion p-value of 0.10 was used for this first step. Significant variables after this stage were then included in a further multivariate analysis of all the remaining covariates. This step was performed to re-assess the effect of each covariate (that was not in the parsimonious model) while accounting for the variables that were most strongly associated with retinopathy. Variables were entered individually into the parsimonious model to check for significance. Rate ratios with 95% confidence intervals were derived for all terms from the coefficients of this reduced model. The most appropriate representation of each variable (section 4.10.5) was used in this step.

4.10.7 Secondary Analysis: Interaction

Secondary analyses investigated plausible interactions. Only one known interaction has been reported in the literature for diabetic retinopathy in a native population.[47] In Lee's study of Oklahoma Indians, a significant interaction was found during multivariate analysis for fasting blood glucose and hypertension. Interestingly, Lee found that when both

variables were represented dichotomously the relationship between fasting blood glucose and retinopathy was stronger when hypertension was not present. The authors did not offer an interpretation of this finding.

For the present study, fasting blood glucose and hypertension were fit to the parsimonious model as dichotomous variables and the interaction term was tested. However, since no other definite interactions were described in the literature, relationships that were defined 'a priori' by the investigators were run using the parsimonious model for exploratory purposes.

The proposed interaction terms, based on postulated associations, included age and fasting blood glucose, sex and fasting blood glucose, age and hypertension, sex and hypertension, age and treatment regimen, and sex and treatment regimen. Dichotomous representations of all variables were used to aid in the interpretation of the results from this section of the analysis.

4.10.8 Secondary Analysis: Poisson Regression

A Poisson multiple regression was fit in an identical manner to the proportional hazards model for the derivation of a parsimonious model. The purpose of this step was to generate coefficients that represented relative risk and to allow a direct comparison between coefficients generated by the Cox's proportional hazards and the Poisson multiple regression models. One problem with fitting the Poisson regression for diabetic retinopathy was that the rare disease assumption was not met.

5.0 RESULTS

5.1 POPULATION STATISTICS

5.1.1 Prevalence of Diabetes in Moose Factory and Moosonee

During the October 1997 data collection visit to Moose Factory and Moosonee, 283 living individuals with diabetes were identified through the two medical clinics. Given the populations of these communities, as estimated by the Health Planning Office of the Weeneeebayko Hospital, the point prevalence for diabetes in Moose Factory and Moosonee was approximately 5.5% (95% CI 4.9% to 6.1%).[61,62] However, this number is not necessarily accurate because Moosonee census data was unavailable, necessitating the use of population estimates for this community. In addition, the Moosonee Clinic's diabetes registry was not up-to-date, preventing identificatin of new patients with diabetes from the past 1 to 2 years (Table 5.1.1). For these reasons, the diabetes prevalence data from Moose Factory was a more internally valid measure (6.2% prevalence, 95% CI 5.3 to 7.2%).

Because the Cree were found to have a larger percentage of their population under the age of 35 when compared to the Canadian population (Table 5.1.2), direct age-standardized diabetes prevalence statistics were calculated for Moose Factory to allow for a more appropriate comparison of diabetes prevalence between these two populations. The direct age-standardized prevalence for Moose Factory was calculated using 1991 Canadian census data for individuals over the age of 15.[63] This value was found to be 103.1 per 1,000 individuals (95% CI 88.6 to 117.6 per thousand) (Table 5.1.2) (The absence of population distribution data for Moosonee did not allow individuals from this community to be included in this estimate.). For the general Canadian population, the estimated prevalence of diabetes is approximately 5%.[1]

5.1.2 Demographic Data for Moose Factory and Moosonee Diabetics

Demographic features of the full cohort are presented in Table 5.1.3. Information on each variable was not available for all subjects. For the independent variables, excluding smoking, data were available for at least 75% of subjects--only 63% had smoking histories recorded in their charts (n=177).

As of December 1997, the average age of individuals with diabetes in Moose Factory and Moosonee was 53 years. The average duration of diabetes was 8.5 years. Sixty-six percent of all those with diabetes were women and the same percentage were on anti-hypertensive medication(s). Most subjects were being treated with oral hypoglycemics and fifteen percent had suffered a myocardial infarction or stroke (Table 5.1.3).

5.1.3 Number of Patients with Eye Examinations

Over the past four years, 241 diabetics from Moose Factory and Moosonee were examined by the retinal specialists participating in the James Bay screening program. Forty-two people with known diabetes in these communities had not been screened for diabetic retinopathy. Overall, an 82.5% screening success rate had been achieved for the four-year screening period.

For the 18 month interval leading up to the last screening visit, 75.5% of known individuals diabetes were examined. In the one-year interval from January 1996 to January 97, 64.3% of the population with diabetes were examined.

5.1.4 Comparison of Patients With and Without Eye Examinations

General features of subjects who had eye examinations were compared with those who did not (Table 5.1.4). Patients who had not been examined were more likely to reside in Moosonee and to have had diabetes for a shorter period of time. These individuals were also less likely to be on insulin.

A trend towards younger age, lower hemoglobin A1C, and lower serum cholesterol levels was also seen in those without eye examinations.

5.1.5 Summary of Data for the Three Categories of Retinopathy

Although the presence or absence of any diabetic retinopathy was the outcome of interest in this study, data was collected for the three main subgroups of retinopathy: background diabetic retinopathy, macular edema, and proliferative diabetic retinopathy. The prevalence of any degree of retinopathy was 34.4% (83/241). Background retinopathy and macular edema were found in 73.5% (61/83) and 21.7% (18/83) of patients with retinopathy respectively. Proliferative retinopathy was a rare finding; only four patients were found to have proliferative disease during the course of the screening process. (Table 5.1.5)

5.1.6 Descriptive Statistics for the 'Limited' Cohort

For the primary objective of this paper, a 'limited' cohort was selected from the larger cohort that included all people with diabetes who had undergone eye examinations. This 'limited' cohort only included individuals with exposure data from years one to six following their diagnosis of diabetes (n=157). Those without data from this time period were compared to the group that had this information in Table 5.1.6.

Significant differences were found between these two groups for almost all variables tested. The 'limited' cohort included individuals who were younger, had a shorter duration of diabetes, and were more likely to be on a dietary treatment regimen. They also had significantly higher BMIs, lower hemoglobin A1C levels, and were more likely to be from Moose Factory. Individuals that were excluded from the limited cohort were more likely to have retinopathy.

Table 5.1.1 Numbers of Subjects (with diabetes) in Each Community

Community	Number of subjects identified from medical clinic charts (percentages)	TOTAL Population of each community
Moose Factory (% of total number of individuals with diabetes)	174 (6.2%) (95% CI 5.3% - 7.2%)	2819
Moosonee (% of total number of individuals with diabetes)	109 (4.7%) (95% CI 3.9% - 5.6%)	2300
TOTALS	283 (5.5%) (95% CI 4.9% - 6.1%)	5119

Table 5.1.2 Direct Standardization of Diabetes Prevalence

Age	Canadian population (%)	Moose Factory population (%)†	Individuals with diabetes in Moose Factory	Age specific prevalence of diabetes (per 1,000)
15-24	3,830,505 (14.03%)	504 (17.9%)	5	9.9
25-34	4,866,580 (17.83%)	519 (18.4%)	15	28.9
35-44	4,371,375 (16.01%)	384 (13.6%)	35	91.1
45-54	2,966,240 (10.87%)	245 (8.7%)	43	175.5
55-64	2,399,625 (8.79%)	104 (3.7%)	41	394.2
65-74	1,895,070 (6.94%)	87 (3.1%)	18	206.9
75-84	991,565 (3.63%)	38 (1.3%)	13	342.1
85+	197,030 (0.72%)	19 (0.7%)	4	210.5
15-85+ Totals	21,517,990 (78.8%)	1,900 (67.3%)	174	91.6
Standardized Rate (per thousand) 103.1				

† The Moose Factory population distribution is presented for comparison purposes. Age standardized-rates for Moose Factory subjects were calculated using the Canadian population distribution as the standard.

Table 5.1.3 Basic Demographic Data for Moosonee and Moose Factory

Demographic Variable	**Subjects (with diabetes)**	**Averages presented for continuous variables** **Number (Percent) presented for dichotomous and categorical variables**	**Standard Deviation**
Total number of subjects	283		
Average age of subjects	282	53 years	15 years
Average duration of diabetes	272	8.5 years	6.3 years
Number of Males/Females	283	96 / 187 (34% / 66%)	
Treatment Regimen Distribution Diet / Oral / Insulin	277	77 / 147 / 53 (28% / 53% / 19%)	
Hypertensives / Normotensives	275	182 / 93 (66% / 34%)	
Smokers Ever / Never	177	88 / 89 (49.7% / 50.3%)	
Stroke or Myocardial Infarction Ever / Never	256	38 / 218 (14.8% / 85.2%)	
Average hemoglobin A1C	260	0.10 %	0.03 %
Average body-mass index	215	32.7 Kg/m^2	5.5 Kg/m^2
Average serum cholesterol	222	5.24 mmol/L	1.08 mmol/L
Average blood urea nitrogen	258	5.4 mmol/L	2.0 mmol/L
Average serum creatinine	259	71.8 mmol/L	27.3 mmol/L

Table 5.1.4 Comparison of Summary Statistics for Those With/Without Eye Examinations (number of data points presented for each variable)

Variables	Patients with eye examinations	Patients without eye examinations	Comparison of groups*† Ho: no difference
Number of diabetics	241	42	Total = 283
Average age as of Dec. 1997 (years) (n = # with data)	54.1 * (n = 241)	47.0 (n = 42)	p = 0.003
Sex (females/males) (%) (n = # with data)	158/83 † (65.6/34.4) (n = 241)	29/13 (69.0/31.0) (n = 42)	p = 0.79
Home Community (# diabetics) (%) (Moose Factory/Moosonee)	155/86 (64.3:35.7) (n = 241)	19/23 (45.2/54.8) (n = 42)	p = .03
Average duration of diabetes as of Dec. 1997 (years) (n = # with data)	9.0 (n = 238)	5.2 (n = 34)	p < 0.0001
Treatment (diet/oral/insulin) (%) (n = # with data)	61/128/52 (25.3/53.1/21.6) (n = 241)	16/19/1 (44.4/52.8/2.8) (n = 36)	p = 0.002
Average body mass index (Kg/m^2) (n = # with data)	32.5 (n = 198)	34.5 (n = 17)	p = 0.20
Average hemoglobin A1C (percent) (n = # with data)	0.104 (n = 228)	0.094 (n = 32)	p = 0.08
Average Serum Cholesterol (mmol/L) (n = # with data)	5.28 (n = 201)	4.84 (n = 21)	p = 0.12
Hypertension (present/absent) (%) (n = # with data)	163/76 (68.2/31.8) (n = 239)	19:17 (52.8/47.2) (n = 36)	p = 0.10

* Mann-Whitney U Test used for comparison in the case of continuous variables
† X^2-test used for categorical variables.
Underlined p-values significant at alpha = 0.05

Table 5.1.5 Frequencies and Percentages of Types of Diabetic Retinopathy in Moose Factory and Moosonee

		Number of subjects with each class of retinopathy	Percentage of each class of retinopathy
No Retinopathy		158	**65.6%**
Retinopathy		83	**34.4%**
	Background Retinopathy	61/83	25.3%
	Macular Edema	18/83	7.5%
	Proliferative Retinopathy	4/83	1.6%
TOTALS		241	**100%**

Table 5.1.6 Summary Statistics: Subjects with exposure data from years 1-6 post diagnosis of diabetes, compared to those without this data.

Variables	Subjects with exposure data from years 1-6	Subjects without exposure data from years 1-6	Comparison of groups*† Ho: no difference
Number of Individuals with Diabetes	157	84	241 Total
Age at eye examination (average years) (n = # with data)	52.5 • (n = 157)	54.1 (n = 84)	p = 0.01
Sex (females/males) (%) (n = # with data)	103/54† (65.6/34.4) (n = 157)	55/29 (65.5/34.5) (n = 84)	p = 0.98
Community (M.Factory/Moosonee) (%) (n = # with data)	109/48 (69.4/30.6) (n = 157)	46/38 (54.8/45.2) (n = 84)	p = 0.02
Duration of diabetes to eye exam (average years) (n = # with data)	4.6 (n = 156)	13.8 (n = 82)	p < 0.0001
Treatment (diet/oral/insulin) (%) (n = # with data)	48/90/19 (30.6/57.3/12.1) (n = 157)	13/38/33 (15.5/45.2/39.3) (n = 84)	p < 0.0001
Body Mass Index (average Kg/m^2) (n = # with data)	33.49 (n = 129)	30.93 (n = 69)	p = 0.004
Hemoglobin A1C (%) (n = # with data)	0.10 (n = 150)	0.11 (n = 78)	p = 0.01
Serum Cholesterol (average mmol/L) (n = # with data)	5.24 (n = 133)	5.37 (n = 68)	p = 0.22
Hypertension (present/absent) (%) (n = # with data)	106/49 (68.4/31.6) (n = 155)	57/27 (67.9/32.1) (n = 84)	p = 0.93
Retinopathy (present/absent) (%)	33/124 (21/79)	50/34 (59.5/40.5)	p < 0.0001

* Mann-Whitney U Test used for comparison in the case of continuous variables
† X^2-test used for categorical variables.
Underlined p-values significant at alpha = 0.05

5.2 RESULTS FOR THE 'LIMITED' COHORT (SUBJECTS WITH EXPOSURE DATA FROM YEARS 1-6 POST DIAGNOSIS OF DIABETES)

5.2.1 Descriptive Statistics for Continuous Variables: Limited Cohort

Figures 5.2.1 to 5.2.13 present descriptive statistics and histograms of continuous covariates for the limited cohort of 157--subjects with data from years one to six following their diagnosis of diabetes. Histograms are presented with an overlayed normal distribution. In addition, basic summary statistics are presented for each variable including: median, range, interquartile range, mean, standard deviation, and missing data counts.

The histograms and summary data were used to give an indication of the normality of each distribution. Large differences between the mean and median, or standard deviations greater than one-half the mean were considered indicators of non-normality. Using these criteria, the distributions for duration of diabetes and for serum triglyceride levels appeared non-normal. Less severe departures from the normal distribution were noted for body-mass index, fasting blood glucose, blood urea nitrogen and serum creatinine. The rest of the continuous variables appeared normally distributed.

The departure from normality that was appreciated for duration of diabetes was likely due to the narrow range of values that the limited cohort demonstrated for this variable--a result of the limited cohort's more rigid inclusion criteria, that were based on specific covariate data availability. Moreover, because a definite date of onset for type 2 diabetes was difficult to ascertain, integers were frequently used for duration of diabetes, limiting the actual number of different values for this variable.

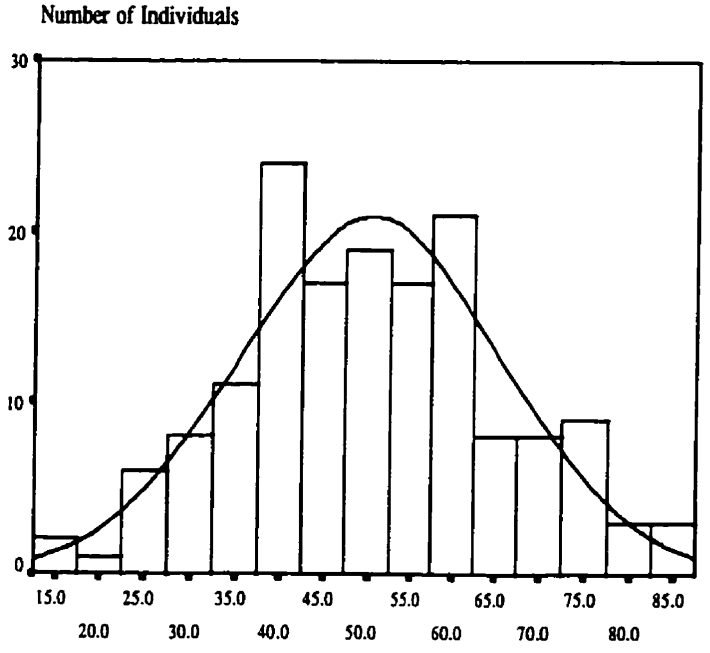
For serum triglycerides, the non-normal distribution appeared to be attributable not only to its right skewed distribution, but also to a cluster of individuals with very similar values within the normal range.

Because of potential problems with the non-normality of duration of diabetes and

serum triglycerides, all analyses in the following sections used non-parametric tests whenever one of these variables was evaluated.

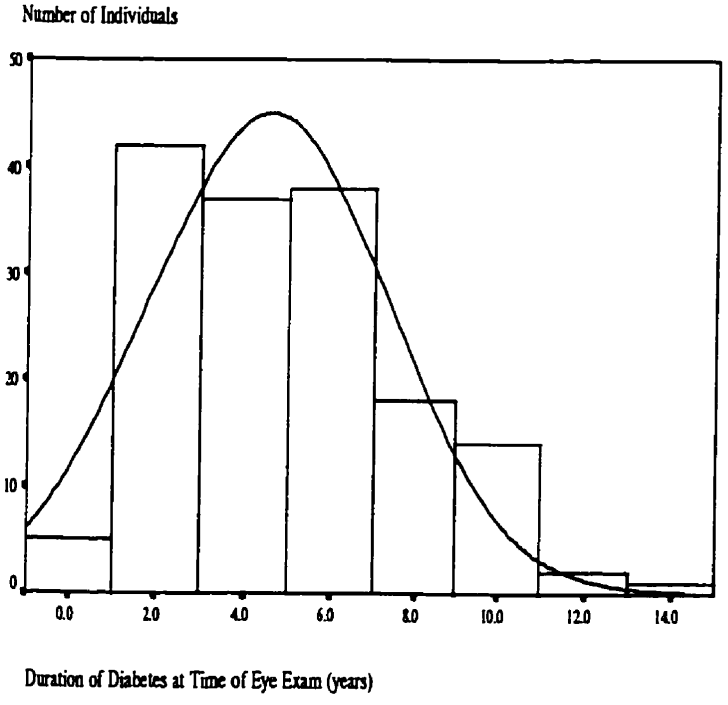
5.2.2 Descriptive Statistics for Dichotomous and Categorical Variables

Tables 5.2.1 to 5.2.7 present data that summarizes the frequencies, percentages, and missing values of each dichotomous and categorical variable. Significant numbers of missing data was most notable for smoking. Also of note was the high number of subjects who were on anti-hypertensive medications--over 68%.



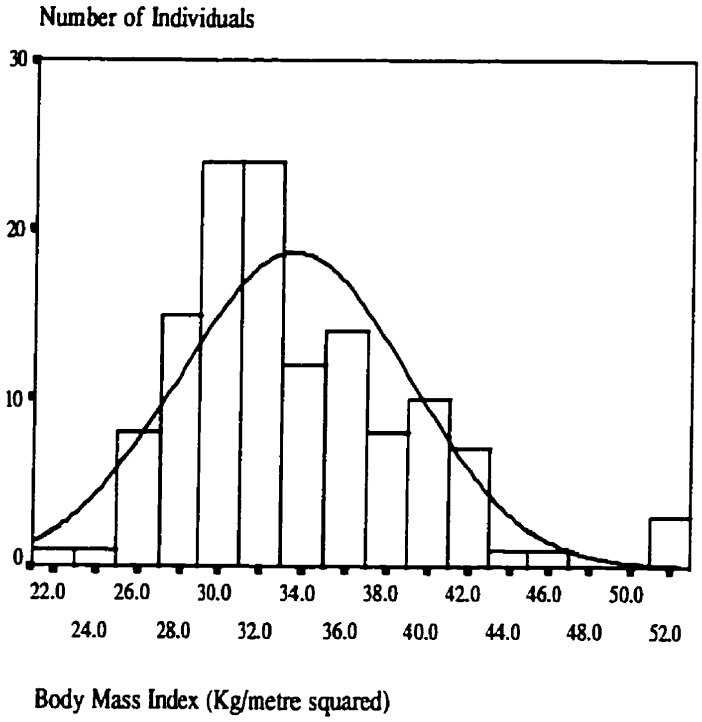
Median			50
Min.	16	Max.	83
25th%	39	75th%	61
Mean			50.5
Std. Dev.			15.0
Valid cases			157
Missing cases			0

Figure 5.2.1



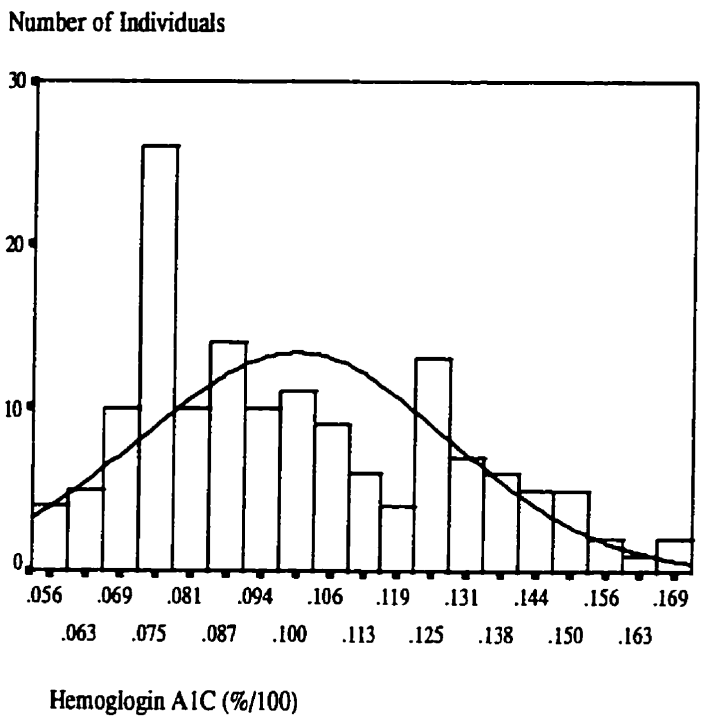
Median			4.0
Min.	0.5	Max.	14.0
25th%	2.0	75th%	6.0
Mean			4.6
Std. Dev.			2.78
Valid cases			157
Missing cases			0

Figure 5.2.2



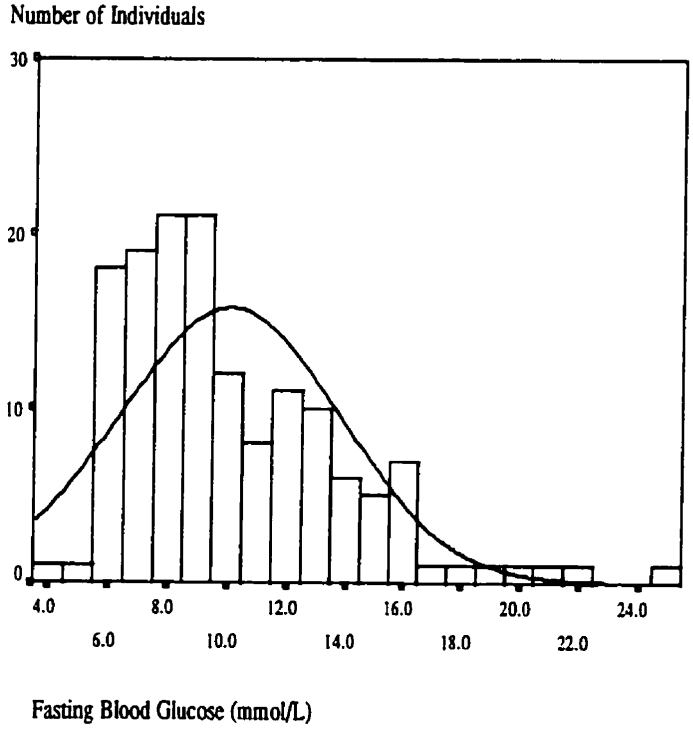
Median			32.3
Min.	21.6	Max.	52.5
25th%	29.6	75th%	36.7
Mean			33.5
Std. Dev.			5.5
Valid cases			129
Missing cases			28

Figure 5.2.3



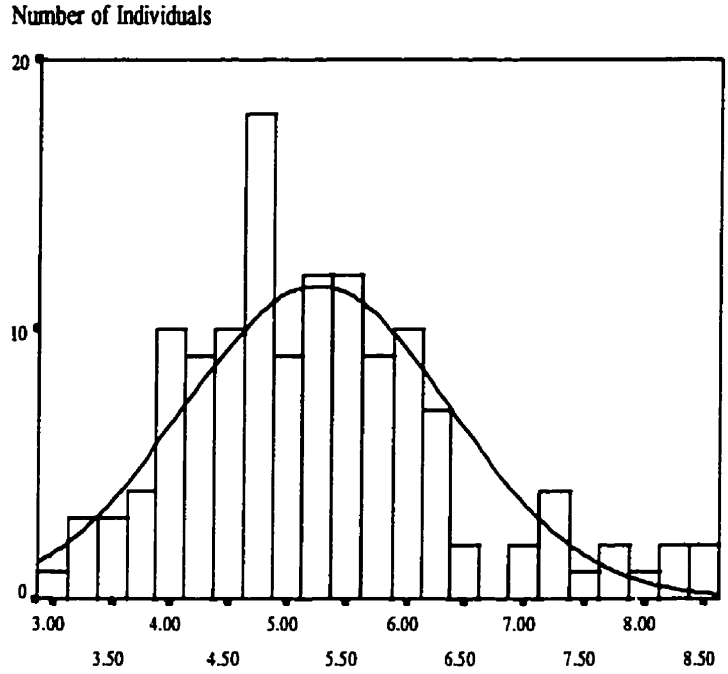
Median			0.094
Min.	0.054	Max.	0.170
25th%	0.077	75th%	0.124
Mean			0.100
Std. Dev.			0.028
Valid cases			150
Missing cases			7

Figure 5.2.4



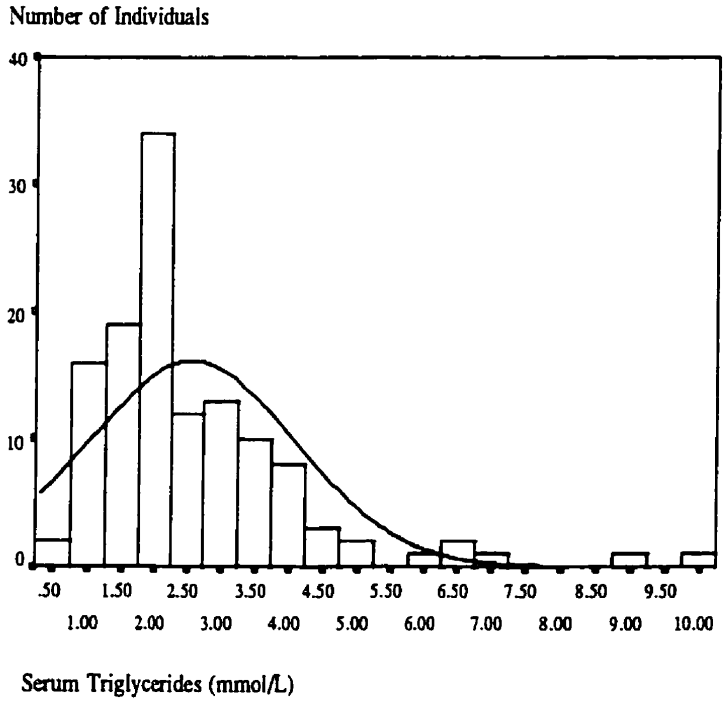
Median			8.9
Min.	4.1	Max.	25.4
25th%	7.3	75th%	12.4
Mean			10.1
Std. Dev.			3.7
Valid cases			147
Missing cases			10

Figure 5.2.5



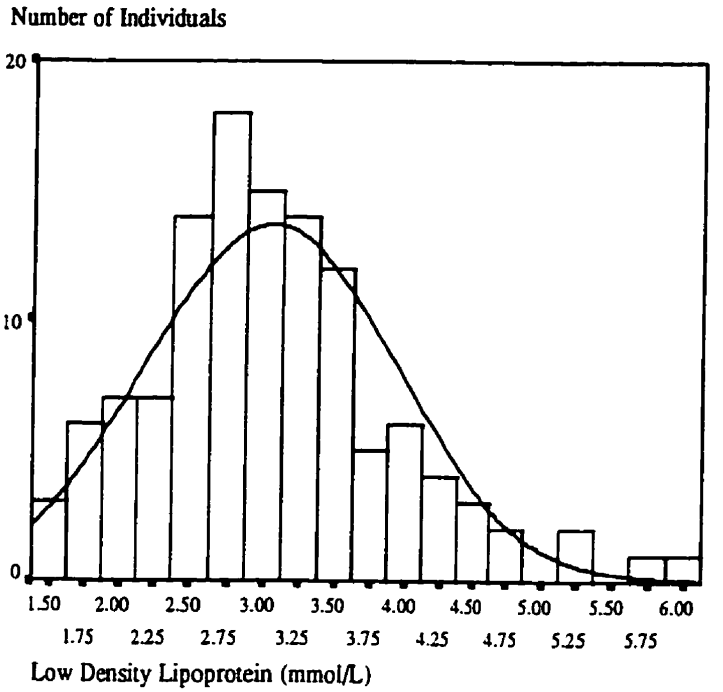
Median			5.10
Min.	3.00	Max.	8.54
25th%	4.43	75th%	5.89
Mean			5.24
Std. Dev.			1.14
Valid cases			133
Missing cases			24

Figure 5.2.6



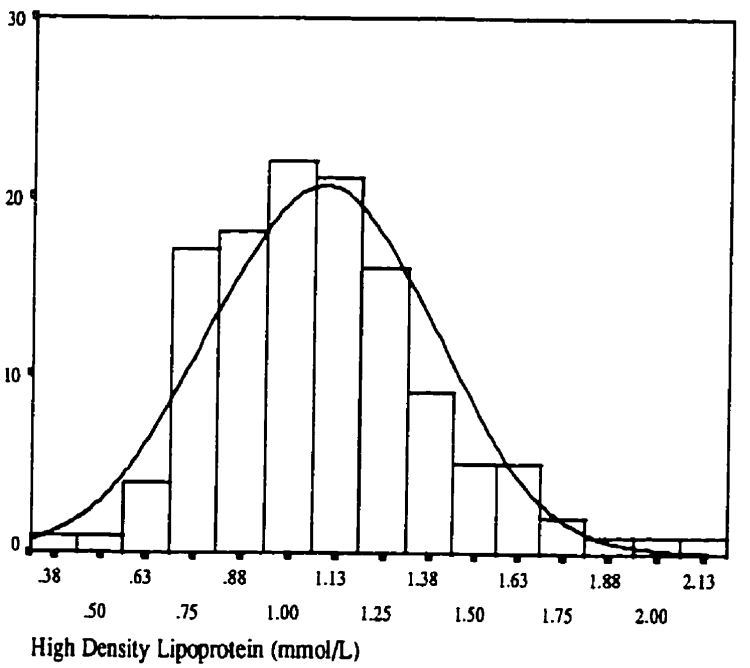
Median			2.14
Min.	0.52	Max.	9.93
25th%	1.61	75th%	3.18
Mean			2.55
Std. Dev.			1.54
Valid cases			125
Missing cases			32

Figure 5.2.7



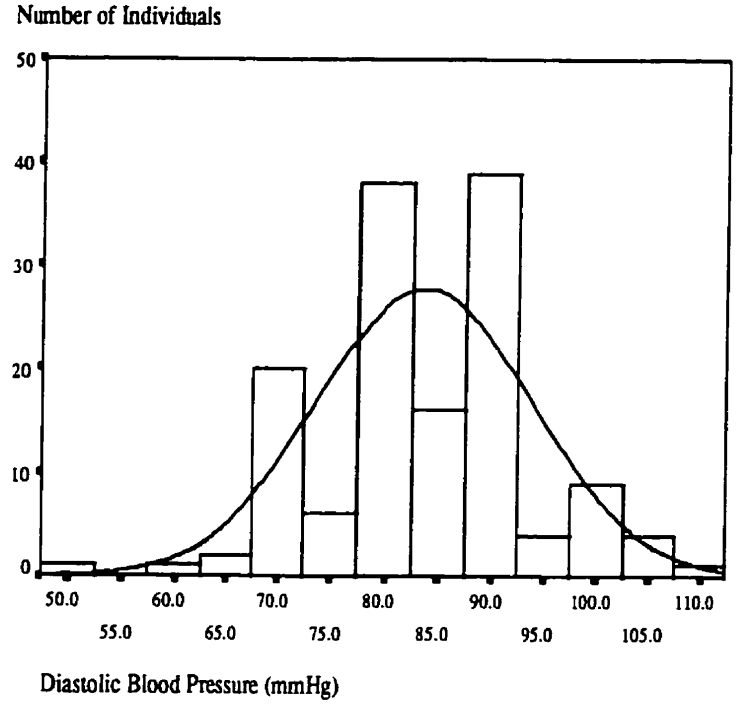
Median		2.98
Min. 1.43	Max.	5.98
25th% 2.50	75th%	3.51
Mean		3.05
Std. Dev.		0.87
Valid cases		120
Missing cases		37

Figure 5.2.8



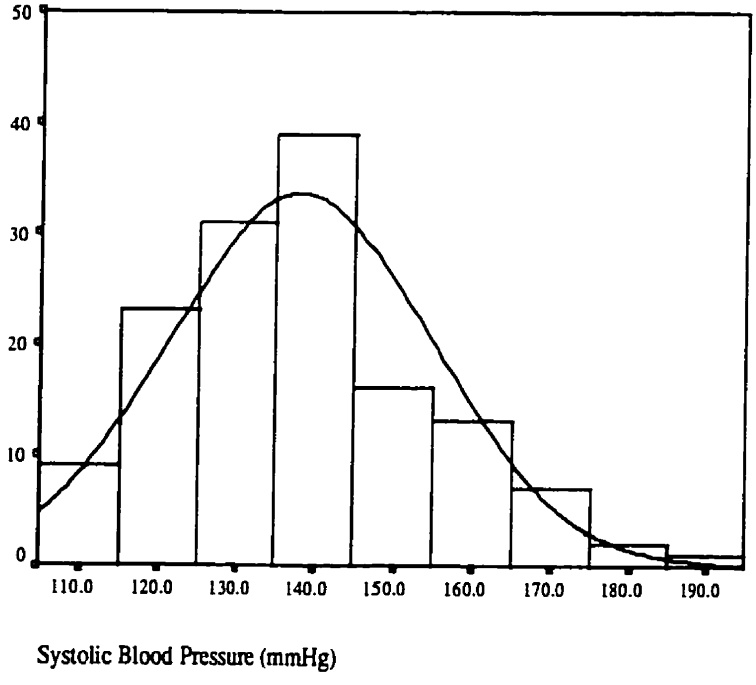
Median		1.05
Min. 0.38	Max.	2.08
25th% 0.88	75th%	1.26
Mean		1.09
Std. Dev.		0.30
Valid cases		124
Missing cases		33

Figure 5.2.9



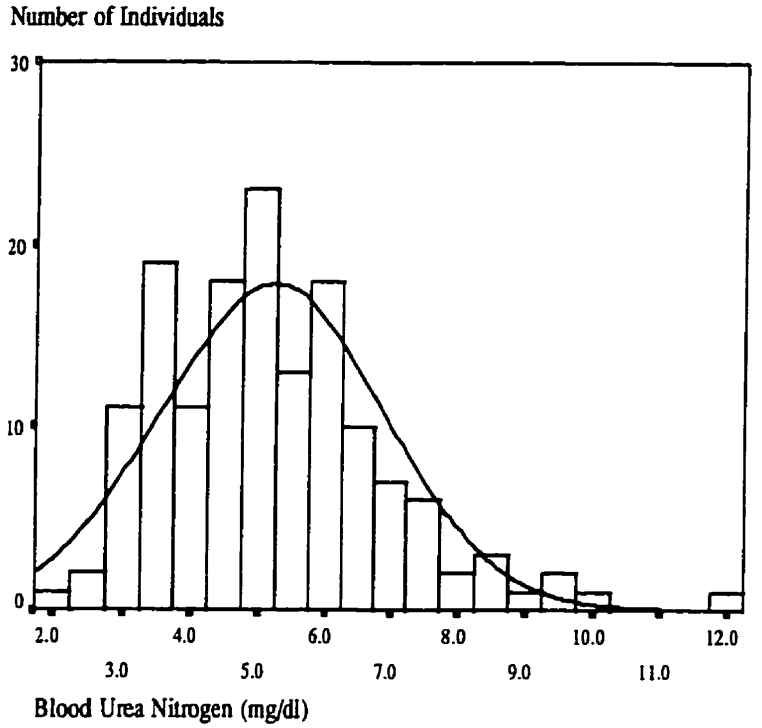
Median		84
Min. 48	Max.	110
25th% 78	75th%	90
Mean		83
Std. Dev.		10
Valid cases		141
Missing cases		16

Figure 5.2.10



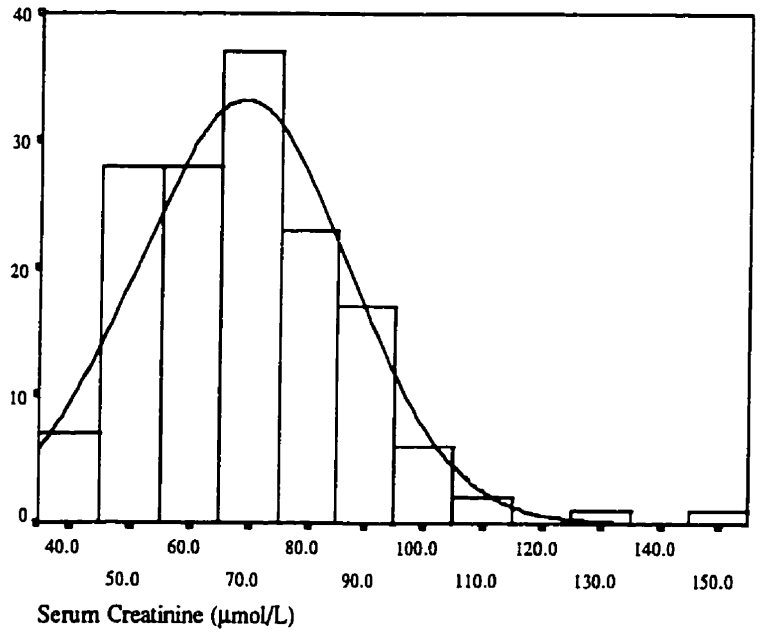
Median		140
Min. 106	Max.	190
25th% 127	75th%	150
Mean		138.0
Std. Dev.		16.7
Valid cases		141
Missing cases		16

Figure 5.2.11



Median			5.1
Min.	2.2	Max.	12.0
25th%	4.0	75th%	6.2
Mean			5.2
Std. Dev.			1.7
Valid cases			149
Missing cases			8

Figure 5.2.12



Median			67.0
Min.	35.0	Max.	145.0
25th%	55.8	75th%	79.3
Mean			68.8
Std. Dev.			18.0
Valid cases			150
Missing cases			7

Figure 5.2.13

Table 5.2.1 Retinopathy

	Frequency	Percent
Present	33	21.0
Absent	124	79.0
Missing Values	-	-
Totals	157	100

Table 5.2.2 Community

	Frequency	Percent
Moose Factory	109	69.4
Moosonee	48	30.6
Missing Values	-	-
Totals	157	100

Table 5.2.3 Sex

	Frequency	Percent
Female	103	65.5
Male	54	34.4
Missing Values	-	-
Totals	157	100

Table 5.2.4 Treatment Regimen

	Frequency	Percent
Diet	48	30.6
Oral Hypoglycemic	90	57.3
Insulin	19	12.1
Missing Values	-	-
Totals	157	100

Table 5.2.5 Hypertension

	Frequency	Percent	Case Percent
Present	106	67.5	68.4
Absent	49	31.2	31.6
Missing Values	2	1.3	-
Totals	157	100	100

Table 5.2.6 Vascular Complications

	Frequency	Percent	Case Percent
Ever	22	81.5	85.3
Never	128	14.0	14.7
Missing Values	7	4.5	-
Totals	157	100	100

Table 5.2.7 Smoking

	Frequency	Percent	Case Percent
Ever	54	34.4	47.8
Never	59	37.6	52.2
Missing Values	44	28.0	-
Totals	157	100	100

5.3 COVARIATE CORRELATIONS AND INTERRELATIONSHIPS

Correlations and associations were examined for all covariates for the purpose of describing the inter-relationships between variables, and to help in the interpretation of the multivariate models. These tests of association were also performed to identify strongly collinear variables.

5.3.1 Correlations for Continuous Variables

Spearman's rank-order and Pearson's product-moment correlation coefficients were calculated for all continuous variables. These results are presented in Table 5.3.1. The correlation table consists primarily of Pearson's correlations except for comparisons involving duration of diabetes and serum triglyceride levels, in which case correlations were obtained using Spearman's rank-order test. Parametric and non-parametric tests were both performed to provide comparative correlation coefficients and p-values for variables that were moderately non-normally distributed (body-mass index, fasting blood sugar, blood urea nitrogen and serum creatinine); however, in almost every circumstance, there were no meaningful differences between the results of these tests.

Significant negative correlations were found between age and hemoglobin A1C, age and fasting blood glucose, and age and diastolic blood pressure. Age was positively correlated with systolic blood pressure, blood urea nitrogen, and serum creatinine. Duration of diabetes was positively correlated with body-mass index, hemoglobin A1C, fasting blood glucose, and serum cholesterol.

Strong correlations were also found between hemoglobin A1C and fasting blood glucose, serum cholesterol and triglycerides, diastolic and systolic blood pressure, and blood urea nitrogen and serum creatinine. A negative correlation was found between fasting blood glucose and the two renal function tests.

All of these correlations do not lend themselves to easy interpretation; however, some of the observed relationships do seem understandable. For example, the decline in renal function status with age was predictable, especially for a population with diabetes. As well, the numerous lab measures that were associated with duration of disease could be attributed to the effect that more advanced diabetes has upon the control of an individual's systemic metabolic state.

Most of the other strong associations observed in this section appeared to relate to variables that were somehow collinear: blood urea nitrogen and serum creatinine, systolic and diastolic blood pressure, serum cholesterol and triglycerides, and hemoglobin A1C and fasting blood glucose. These correlations were understandable since these variable pairs measure very similar physiologic parameters.

More puzzling significant results included the negative correlation found between fasting blood sugar and the two renal function tests. Age may have confounded this relationship since younger individuals tended to have higher fasting blood glucose levels and more normal renal function tests.

There were other correlations that also did not appear readily explicable; however, because many tests were being conducted simultaneously, there may have been significant correlations that were simply due to the multiple comparisons being performed. Moreover, since these tables are primarily exploratory, there is less need to account for every significant correlation.

5.3.2 Associations: Continuous and Dichotomous Variables

This section describes the relationships between continuous and dichotomous variables. Table 5.3.2 presents Student's t-test results for these comparisons. The non-parametric Mann-Whitney U test results are also presented for duration of diabetes and

serum triglycerides. In this section, as in section 5.3.1, the non-parametric and parametric tests produced essentially the same results.

Women were found to have elevated high density lipoprotein levels, lower diastolic blood pressures and lower renal function tests. These changes might relate to the protective systemic-vascular status of women, or improved female compliance with dietary and medical advice.

As might have been expected, hypertensive individuals were older, and had poorer renal function tests. They were also found to have lower fasting blood glucose levels and higher blood pressure measurements than non-hypertensives. The association between hypertension and lower fasting blood glucose levels was less intuitively understandable.

Smokers tended to be younger and had lower high density lipoprotein levels than non-smokers. Those with vascular complications were significantly older than those without.

5.3.3 Associations: Treatment Regimen and All Other Variables

Table 5.3.3 presents the associations between treatment regimen, the only categorical variable in this data set, and the other continuous variables. As with sections 5.3.2 and 5.3.1, parametric and non-parametric tests were used to assess these relationships. One-way and Kruskall-Wallis analysis of variance (ANOVA) tests revealed exactly the same significant associations for all variables.

The main univariate associations that were found with treatment regimen were duration of diabetes, hemoglobin A1C, and fasting blood glucose levels. A post-hoc examination of significant ANOVA tests was carried out to determine which categories of treatment regimen were different for each continuous variable. The Bonferroni test indicated that individuals on dietary management had significantly shorter durations of

diabetes, lower hemoglobin A1C levels, and lower fasting blood glucose levels than those on oral hypoglycemics or insulin. (Table 5.3.4)

These results suggest that in the early stages of diabetes, blood sugar measures may be more easily controlled by diet alone. Similarly, individuals with diet controlled diabetes may have less aggressive, more manageable disease states than those on medical therapies.

An association between treatment regimen and duration of diabetes may explain differences in treatment status between the limited cohort and the full cohort. They may also explain differences in treatment regimen for those who underwent ocular examinations and those who did not (section 6.2.4).

Associations between treatment status and the dichotomous variables are presented in the last column of Table 5.3.5. No significant associations were found using a chi-square test (X^2) without a continuity correction for a two-by-three table.

5.3.4 Comparison of Dichotomous and Categorical Variables

Chi-square tests, with continuity corrections, were used to examine associations between dichotomous variables. The only significant association in this comparison was between smoking and hypertension. Individuals who did not smoke were more likely to be hypertensive (Table 5.3.5). This somewhat counter-intuitive relationship between smoking and hypertension may be related to the fact that smokers were significantly younger than non-smokers.

Table 5.3.1 Correlations Between Continuous Variables (Pearson's product-moment correlation coefficient, r) Grey rows/columns indicate non-normally distributed variables assessed with Spearman's rank-order test.

	1	2	3	4	5	6	7	8	9	10	11	12	13
Age at eye exam (1)	1	.13* 156^ .09~	-.12 129 .16	-.18 150 .03	-.29 147 <.01	.10 133 .26	-.06 125 .50	.17 120 .07	.16 124 .07	.38 141 <.01	-.17 141 .05	.50 149 <.01	.29 150 <.01
Duration of Diabetes (2)		1	-.17 129 .05	.282 150 <.01	.185 146 .03	.179 133 .04	.013 125 .89	.078 120 .40	.145 124 .11	.031 140 .72	.011 140 .90	.103 149 .21	-.08 150 .33
Body mass index (3)			1	-.06 125 .48	-.05 126 .52	-.16 116 .08	0.06 112 .54	-.13 107 .19	-.23 111 .02	.07 117 .45	.01 117 .31	-.08 124 .38	-.01 125 .93
Hemoglobin A1C (4)				1	.59 142 <.01	.19 132 .03	.196 124 .03	-.03 119 .78	-.11 123 .23	-.077 136 .37	.15 136 .07	-.12 146 .17	-.064 147 .44
Fasting blood sugar (5)					1	.13 129 .20	.21 123 .02	-.12 118 .20	-.10 122 .29	-.14 133 .12	.18 133 .04	-.23 142 <.01	-.27 143 <.01
Cholesterol (6)						1	.37 124 <.01	.80 119 <.01	.30 124 <.01	.25 124 <.01	.08 124 .36	.16 131 .08	.14 132 .12
Triglycerides (7)							1	.075 120 .41	-.350 123 <.01	.036 119 .69	.108 119 .24	-.052 123 .57	.088 124 .33
Low density lipoprotein (8)								1	.20 119 .03	.25 114 <.01	.07 114 .45	.27 118 <.01	.17 119 .07
High density lipoprotein (9)									1	.14 118 .13	.036 118 .70	.13 122 .15	-.07 123 .42
Systolic blood pressure (10)										1	.39 141 <.01	.16 137 .07	.12 138 .16
Diastolic blood pressure (11)											1	-.16 137 .06	-.08 138 .35
Blood urea nitrogen (12)												1	.57 149 <.01
Creatinine (13)													1

* correlation coefficient

^ number of subjects

Underlined p-values significant at alpha = 0.05

~ p-value

Table 5.3.2 Student t-test for Associations Between Categorical and Continuous Variables (Grey rows are t-test results for non-normally distributed variables – analysed by the Mann-Whitney U test.)

Variables	Community	Sex	Hypertension	Smoking	Vascular Complications
Age at eye exam	0.35* 155^ 0.73~	0.18 155 0.85	-4.37 153 <u>≤0.001</u>	3.39 111 <u>0.001</u>	-3.96 148 <u>≤0.001</u>
Duration of diabetes	2310.5† 0.24	2551.5 0.40	2222.5 0.15	1416.5 0.31	1071.0 0.07
Body mass index	2.43 127 <u>0.02</u>	-0.44 127 0.657	-0.91 126 0.37	-1.19 98 0.24	0.18 36.2 (uneq.var.) 0.86
Hemoglobin A1C	0.27 148 0.79	0.39 83.9 (uneq. var.) 0.70	1.25 146 0.21	-1.48 110 0.14	0.29 142 0.78
Fasting blood glucose	-1.38 145 .17	0.04 145 0.97	2.49 143 <u>0.01</u>	-1.33 109 0.19	0.87 139 0.39
Cholesterol	0.53 131 0.60	0.07 131 0.95	-0.05 130 0.96	-0.33 102 0.75	-0.62 126 0.54
Triglycerides	1298.0 0.46	1527.5 0.22	1551.0 0.78	1018.0 0.15	740.5 0.24
Low density lipoprotein	0.82 118 0.42	0.14 118 0.89	-0.67 118 0.50	-0.64 94 0.52	-0.20 116 0.84
High density lipoprotein	-1.32 122 0.06	-2.67 122 <u>0.01</u>	-1.22 122 0.23	2.70 95 <u>0.01</u>	1.06 120 0.29
Systolic blood pressure	1.49 139 0.14	0.38 139 0.71	-3.51 139 <u>0.001</u>	1.18 100 0.24	-0.63 138 0.53
Diastolic blood pressure	-0.52 139 0.61	2.17 139 <u>0.03</u>	-1.86 139 0.07	0.49 94.6 (uneq. var.) 0.63	1.93 138 0.06
Blood urea nitrogen	1.13 147 0.26	2.15 147 <u>0.03</u>	-2.18 146 <u>0.03</u>	1.58 108 0.12	-1.53 140 0.13
Creatinine	2.02 148 <u>0.05</u>	4.6 148 <u>≤0.001</u>	-2.22 147 <u>0.03</u>	0.14 109 0.89	-0.49 141 0.62

* t-statistic
(uneq. var.) unequal variance t-test calculated
<u>Underlined</u> p-values significant at alpha = 0.05
^ degrees of freedom
~ p-value for two-tailed student t-test
† U-statistic

Table 5.3.3 Analysis of Variance: Continuous Variables' Association with Treatment Regimen

Non-parametric test (Kruskall-Wallis) is presented on the right.
(Non-normally distributed variables are presented in grey.)

Variable	Sum of Squares (between/error)	Degrees of Freedom (between/error)	F-statistic	p-value	Kruskall-Wallis X^2	p-value
Age at eye exam	743.6 / 34,173.6	2 / 154	1.68	0.19	2.77	0.25
Duration of diabetes	93.0 / 1,110.9	2 / 154	6.45	0.002	12.17	0.002
Body mass index	21.0 / 3,879.0	2 / 126	0.34	0.71	1.23	0.54
Hemoglobin A1C	0.01 / 0.1	2 / 147	8.87	≤0.001	16.79	≤0.001
Fasting blood glucose	293.9 / 1730.2	2 / 144	12.23	≤0.001	24.69	≤0.001
Cholesterol	4.9 / 166.7	2 / 130	1.90	0.15	2.36	0.31
Triglycerides	2.9 / 289.8	2 / 122	0.61	0.55	0.42	0.81
Low density lipoprotein	0.6 / 89.6	2 / 117	0.40	0.67	0.31	0.86
High density lipoprotein	0.01 / 11.1	2 / 121	0.08	0.93	0.49	0.78
Systolic blood pressure	164.9 / 38,876.0	2 / 138	0.29	0.75	0.48	0.79
Diastolic blood pressure	81.0 / 14,209.3	2 / 138	0.39	0.68	0.96	0.62
Blood urea nitrogen	1.8 / 406.0	2 / 146	0.32	0.72	0.15	0.93
Creatinine	75.0 / 48,221.0	2 / 147	0.11	0.89	0.39	0.82

Underlined p-values significant at alpha = 0.05

Table 5.3.4 Bonferroni Post-hoc Comparisons of Treatment Categories: Means are presented, for the continuous variables in the first column, for each category of treatment.

Variable	Dietary Treatment	Oral Hypoglycemics	Insulin
Duration of Diabetes	3.542*	4.833	5.947
Fasting Blood Glucose	7.964*	10.799	11.835
Hemoglobin A1C	0.0857*	0.1044	0.1106

* Significantly different than the other two means

Table 5.3.5 Dichotomous and Categorical Variable Associations (X^2-Tests performed with and without continuity correction)

	Sex	Community	Hypertension	Smoking	Vascular Complications	Treatment Regimen
Sex	-	0.825* (0.527)*	0.277 (0.118)	0.121 (0.023)	0.055 (<0.001)	2.61
		0.36 † (0.46)†	0.60 (0.73)	0.73 (0.88)	0.82 (1.0)	0.27
Community		-	0.192 (0.064)	0.0087 (0.000)	0.00039 (0.000)	0.482
			0.66 (0.80)	0.93 (1.0)	0.98 (1.0)	0.79
HTN			-	5.06 (4.17)	1.94 (1.30)	1.12
				<u>0.025</u> (0.04)	0.16 (0.25)	0.57
Smoking				-	0.493 (0.186)	0.326
					0.48 (0.67)	0.85
Vascular Complica-tions					-	0.127
						0.94
Treatment Regimen						-

* Chi-square test statistic
<u>Underlined</u> p-values significant at alpha = 0.05
() continuity correction for 2x2 tables
† p-value

Note: treatment categories were analysed as a 2x3 table, hence no continuity correction is presented.

5.4 VARIABLE CONCEPTUALIZATION AND ASSOCIATIONS (UNIVARIATE) WITH DIABETIC RETINOPATHY

5.4.1 Variable Conceptualization for Continuous Variables

Before examining the univariate associations between each covariate and diabetic retinopathy, continuous variables were first considered in a number of different representations. Variable conceptualization analyses were performed to ensure that the most appropriate form of each covariate was used for the ensuing univariate and multivariate analyses (Table 5.4.1). Continuous, dichotomous and quartile representations were considered.

Log-likelihood ratio testing showed that continuous representations were most appropriate for the following variables: duration of diabetes, body-mass index, hemoglobin A1C, and low density lipoprotein. Fasting blood glucose, cholesterol, triglycerides, high-density lipoprotein, diastolic blood pressure and blood urea nitrogen were all best represented as dichotomous factors. Quartile representations demonstrated the lowest p-values on likelihood ratio testing for systolic blood pressure, blood urea nitrogen, and low density lipoprotein.

The use of a continuous representation for duration of diabetes was somewhat of a concern because this variables did not demonstrate a strongly normal distribution in section 5.2; nonetheless, since the strongest representation for duration of diabetes was continuous, and since independent variables in a Cox's model do not have to meet normality assumptions, this form was used in the proportional hazard models.

5.4.2 Continuous Variable Associations with Diabetic Retinopathy

Table 5.4.2 presents the univariate relationships between the most appropriate representation of each continuous variable, as determined in section 5.4.1, and diabetic

retinopathy. Significant associations with retinopathy were found for duration of diabetes, body-mass index, hemoglobin A1C, fasting blood sugar, and serum cholesterol. Body-mass index was the only variable of these that had an inverse association with retinopathy.

5.4.3 Categorical and Dichotomous Variables, Associations with Retinopathy

Relative risks for the development of retinopathy are presented for categorical and dichotomous variables in Table 5.4.3. No significant univariate associations were found for any of the dichotomous variables; yet, insulin therapy demonstrated a strong association with diabetic retinopathy when compared with diet (baseline).

Table 5.4.1 Univariate Associations with Diabetic Retinopathy: Continuous Variable Assessment

Variables	Number	Continuous Representation		Dichotomous Representation		Categorical Representation	
		LR	p-value	LR	p-value	LR	p-value
Age at eye exam	157	0.031	0.86	0.433	0.51*	0.125	0.99
Duration of diabetes	157	3.932	0.047*	2.641	0.10	2.76	0.43
Body-mass index	129	6.305	0.012*	3.999	0.046	6.653	0.08
Hemoglobin A1C	150	7.090	0.008*	5.433	0.02	5.325	0.15
Fasting blood glucose	147	6.695	0.01	8.143	0.004*	7.029	0.07
Cholesterol	133	6.447	0.011	6.624	0.010*	7.739	0.05
Triglycerides	125	0.768	0.38	0.791	0.37*	0.685	0.88
Low-density lipoprotein	120	1.641	0.20	1.614	0.20	4.842	0.18*
High-density lipoprotein	124	0.909	0.34	1.978	0.16*	2.394	0.50
Diastolic blood pressure	141	0.0001	0.99	0.563	0.45*	0.919	0.82
Systolic blood pressure	141	0.159	0.69	0.046	0.83	5.727	0.13*
Blood urea nitrogen	149	0.189	0.66	0.642	0.42	4.895	0.18*
Creatinine	150	0.171	0.68	0.651	0.42*	0.688	0.88

* best representation of variable
Underlined p-values significant at alpha = 0.05

Table 5.4.2 Univariate Relative Risks: Continuous Variables and Retinopathy

Variable	Representation	Covariate Unit Interval for the Relative Risk	At Risk 'n'	Evants 'n'	Relative Risk (95% CI)
Age	dichotomous (mean = 50.5 years)	Baseline	82	18	1.00
		Elevated	75	15	0.91 (0.46-1.81)
Duration of diabetes	continuous	10 year interval	157	-	1.17 (1.04-10.00)
Body Mass Index	continuous	5 Kg/m^2 interval	129	-	0.61 (0.40-0.92)
Hemoglobin A1C	continuous	0.01% interval	150	-	1.17 (1.05-1.32)
Fasting Blood Glucose	dichotomous (mean = 10.1 mmol/L)	Baseline	87	10	1.00
		Elevated	60	15	2.90 (1.36-6.20)
Cholesterol	dichotomous (mean = 5.24 mmol/L)	Baseline	72	8	1.00
		Elevated	61	19	2.80 (1.23-6.40)
Triglycerides	dichotomous (mean = 2.55 mmol/L)	Baseline	78	14	1.00
		Elevated	47	12	1.42 (0.66-3.08)
Low Density Lipoprotein	quartiles	Baseline	30	6	1.00
		2nd quartile vs. 1st	32	4	0.63 (0.18-2.22)
		3rd quartile vs. 1st	28	4	0.71 (0.20-2.53)
		4th quartile vs. 1st	30	11	1.83 (0.68-4.96)
High Density Lipoprotein	dichotomous (mean = 1.09 mmol/L)	Baseline	67	10	1.00
		Elevated	57	15	1.76 (0.79-3.93)
Diastolic Blood Pressure	dichotomous (mean = 84 mmHg)	Baseline	69	14	1.00
		Elevated	72	19	1.30 (0.65-2.59)
Systolic Blood Pressure	quartiles	Baseline	35	12	1.00
		2nd quartile vs. 1st	35	5	0.42 (0.15-1.18)
		3rd quartile vs. 1st	35	5	0.42 (0.15-1.18)
		4th quartile vs. 1st	36	11	0.89 (0.39-2.02)
Blood Urea Nitrogen	quartiles	Baseline	36	10	1.00
		2nd quartile vs. 1st	37	4	0.39 (0.12-1.24)
		3rd quartile vs. 1st	34	6	0.64 (0.23-1.75)
		4th quartile vs. 1st	42	12	1.03 (0.44-2.38)
Serum Creatinine	dichotomous	Baseline	81	15	1.00
		Elevated	69	17	1.33 (0.66-2.66)

'Baseline': lowest quartile for quartile representations, below mean for dichotomous representations

Underlined p-values significant at alpha = 0.05

Table 5.4.3 Univariate Associations for Dichotomous/Categorical Variables and Retinopathy

Variables	Categories	At Risk 'n'	Events*	Relative Risk (95% Confidence Interval)
Sex	Male	54	13	1.00
	Female	103	20	0.81 (0.40-1.62)
Community	Moosonee	48	10	1.00
	Moose Factory	109	23	1.03 (0.48-2.13)
Treatment Regimen	Baseline (Diet)	48	5	1.00
	Oral Hypoglycemic	90	21	2.24 (0.85-5.94)
	Insulin	19	7	3.53 (1.12-11.14)
Hypertension	Absent	49	13	1.00
	Present	106	20	0.71 (0.35-1.43)
Vascular Complications	Absent	128	29	1.00
	Present	22	4	0.80 (0.28-2.28)
Smoking	Never	59	14	1.00
	Ever	54	12	0.94 (0.43-2.03)

* Events are defined as the presence of diabetic retinopathy
Underlined p-values significant at alpha = 0.05

5.5 PROPORTIONAL HAZARDS MODEL

5.5.1 Developing a Parsimonious Model

A stepwise procedure was performed to arrive at a parsimonious model that would be used for the adjusted analysis (Section 5.5.2). Modeling all 18 factors was problematic because of missing data for some variables. To maximize the number of subjects used in this process and to preserve degrees of freedom, only factors meeting a liberal 0.10 p-value on univariate analysis were included. These six variables were body-mass index, serum cholesterol, duration of diabetes, fasting blood glucose, hemoglobin A1C, and treatment regimen. For these variables there were 114 individuals with complete data.

The results of this stepwise procedure are presented in Table 5.5.1. The three variables that remained in the final parsimonious model were significant at the 0.10 level for the stepwise procedure. These included body mass index, treatment regimen, and serum cholesterol level. Interestingly, duration of diabetes, perhaps the strongest known predictor for retinopathy, did not make it into the parsimonious model. This may have been due to the selection process used for the limited cohort--individuals without lab data for years one to six following the diagnosis of diabetes were excluded. Subjects with a longer duration of diabetes, who were less likely to have had the advanced lipid and glucose tests performed in the 1970s and early 1980s, were not included in the limited cohort. As a result, duration of diabetes for individuals in the limited cohort may not have spanned a large enough interval to been significant at the 0.10 level.

As mentioned, the decision to limit the derivation of the parsimonious model to six terms was based on concerns about missing data. Values for 19 variables were collected making it likely that many individuals would have missing data for at least one variable. Of the 157 people in the limited cohort, the number with complete data for all exposures was 78. If smoking data was not considered, the number of patients with full data jumped to

97. For the six variables that demonstrated significant univariate associations with retinopathy, there were 114 individuals with complete data.

Two variables that had a particularly large number of missing values included smoking and low density lipoprotein levels. Smoking was poorly recorded in most patient charts and low density lipoprotein was not calculable when triglyceride levels were very high. Smoking had the added problem of its ever / never categorization, a somewhat inexact way of describing this exposure.

A final advantage of using only the six significant univariate terms for deriving the parsimonious model was that many variables were potentially collinear. For example, variables such as systolic and diastolic blood pressures measure similar physiologic processes; moreover, as demonstrated in Section 5.3.1, these variables were also highly correlated. Similar relationships would be expected for the serum lipid studies and the renal function tests. As a result, collinearity could have affected the construction of a parsimonious model based on all 19 variables. Even with the use of only six variables collinearity was potentially a problem because univariate analyses demonstrated that fasting blood sugar and hemoglobin A1C were highly correlated, as were duration of diabetes and hemoglobin A1C (section 5.3.1).

One criticism of the use of only six variables for the creation of the parsimonious model is that the confounding effects of all possible variables is not taken into consideration in the stepwise procedure. However, it is unlikely that variables that were weakly associated with retinopathy on univariate analysis would be strong confounders.

For comparison purposes a second stepwise procedure was performed involving 18 variables, excluding smoking. Only 97 patients had data for all 18 variables; yet, the same factors were ultimately included in the final model--at a liberal p-value of 0.15 for inclusion. These results are presented in Table 5.5.2.

5.5.2 Assessment of Covariates in the Parsimonious Model

This step was performed to reassess the relative risks of each variable for diabetic retinopathy while adjusting for serum cholesterol, body-mass index and treatment regimen. Adjusted associations between retinopathy and each covariate are presented in Table 5.5.3.

For the three variables in the parsimonious model, the calculated relative risks were derived from coefficients that were generated by fitting these three variables in a model on their own. Hence, these relative risks are slightly different from those generated when the parsimonious model was created due to the availability of more subjects.

No variables were significantly associated with diabetic retinopathy on adjusted analysis except for the variables that were in the parsimonious model. Significant associations included body-mass index, insulin treatment, and serum cholesterol level. Increasing levels of BMI were associated with a decreased risk of retinopathy (RR 0.64 for a five unit increase in BMI kg/m^2). Insulin treatment increased the risk of retinopathy when compared to dietary treatment (RR = 4.71). Elevated serum cholesterol levels increased the risk of retinopathy for individuals with a cholesterol level above the population's mean--compared to an individual with a serum cholesterol below the population's mean (mean: 5.2 mmol/L) (RR 2.38).

Table 5.5.1 Results of Stepwise Procedure (identifying the parsimonious model predicting retinopathy)

Variable	Representation	Number of subjects	p-value
Body Mass Index	5 unit intervals	114	0.05
Cholesterol	Baseline (below mean)	59	0.07
	Elevated (above mean)	55	
Treatment	Baseline (Diet)	38	
	Oral vs. Diet	68	0.08
	Insulin vs. Diet	13	0.03

Underlined p-values significant at alpha = 0.05

Table 5.5.2 Stepwise Procedure for all 18 Variables (excluding smoking)

Variable	Representation	Number of Subjects	p-value
Body Mass Index	5 unit intervals	97	0.056
Cholesterol	Baseline (below mean)	51	0.11
	Elevated (above mean)	46	
Treatment	Baseline (Diet)	30	
	Oral vs. Diet	56	0.07
	Insulin vs. Diet	11	0.057
All other variables did not reach significance at the 0.15 level			

Underlined p-values significant at alpha = 0.05

Table 5.5.3 Relative Risks Adjusted for Factors in the Parsimonious Model

Variable	Reference level	Number At Risk	Events (retinopathy)	Relative Risk (95% CI)
Age at eye exam	Baseline (below mean)	82	18	1.00
	Elevated (above mean)	75	15	1.38 (0.62-3.07)
Duration of diabetes	10 year interval	116	-	1.40 (0.33-5.88)
Body-mass Index	5 unit levels (Kg/m^2)	116	-	0.64 (0.04-1.00)
Hemoglobin A1C	0.01 % intervals	115	-	1.02 (0.88-1.19)
Fasting Blood Sugar	Baseline (below mean)	67	10	1.00 (0.49-2.83)
	Elevated (above mean)	48	15	1.18
Cholesterol	Baseline (below mean)	61	7	1.00
	Elevated (above mean)	55	18	2.38 (0.98-5.79)
Triglycerides	Baseline (below mean)	71	13	1.00
	Elevated (above mean)	40	11	1.16 (0.49-2.72)
Low-density lipoprotein	Baseline	28	6	0.99 (0.60-1.67)
	2nd quartile vs. 1st	29	4	0.57 (0.15-2.09)
	3rd quartile vs. 1st	23	3	0.40 (0.09-1.78)
	4th quartile vs. 1st	26	10	0.88 (0.26-3.01)
High-density lipoprotein	Baseline (below mean)	60	9	1.00
	Elevated (above mean)	51	15	1.28 (0.53-3.09)
Systolic Blood Pressure	Baseline	22	7	1.00
	2nd quartile vs. 1st	22	4	0.72 (0.21-2.45)
	3rd quartile vs. 1st	21	5	0.92 (0.29-2.94)
	4th quartile vs. 1st	19	9	1.66 (0.61-4.56)
Diastolic Blood Pressure	Baseline (below mean)	55	11	1.00
	Elevated (above mean)	54	14	1.36 (0.61-3.02)
Blood Urea Nitrogen	Baseline	24	6	1.00
	2nd quartile vs. 1st	33	4	0.58 (0.16-2.11)
	3rd quartile vs. 1st	29	5	0.75 (0.23-2.52)
	4th quartile vs. 1st	28	10	1.36 (0.49-3.76)
Creatinine	Baseline (below mean)	64	11	1.00
	Elevated (above mean)	51	14	1.48 (0.67-3.27)

* Adjusted for serum cholesterol, body-mass index, and treatment regimen

Underlined p-values significant at alpha = 0.05

Table 5.5.4 Relative Risks Adjusted for Factors in the Parsimonious Model (dichotmous variables at data colletion)

Variable	Reference level/units for RelativeRisk	Number at Risk	Events*	Relative Risk† (95% CI)
Sex	Male	37	8	1.000
	Female	79	17	1.169 (0.499-2.737)
Community	Moosonee	22	5	1.000
	Moose Factory	94	20	0.772 (0.276-2.161)
Treatment Regimen	Baseline (Diet)	34	3	1.00
	Oral vs. Diet	68	16	3.058 (0.882-10.60)
	Insulin vs. Diet	14	6	4.711 (1.158-19.16)
Vascular Complications	Present	97	21	1.000
	Absent	16	4	1.021 (0.345-3.029)
Hypertension	Present	33	7	1.000
	Absent	83	18	1.084 (0.447-2.633)
Smoking	Never	47	13	1.00
	Ever	46	9	0.958 (0.391-2.349)

* An event is defined as the presence of diabetic retinopathy
† Adjusted for serum cholesterol, body-mass index, and treatment regimen
Underlined p-values significant at alpha = 0.05

5.6 SECONDARY ANALYSES

To address the secondary objectives of this paper, interaction terms were investigated for diabetic retinopahy and a comparative analysis was performed using Poisson regression as an alternative to the Cox's proportional hazards model.

5.6.1 Assessment of Interaction

Interaction terms from an 'a priori' consideration of possible effect modifiers were examined in the parsimonious model that also included the interaction term's corresponding first order variables. The power of this interaction assessment was very weak and did not demonstrate any significant interactions (Table 5.6.1). Nonetheless, this was an exploratory analysis and a trend was appreciated for the interaction involving age and treatment regimen.

When the individual interaction cells were analysed for treatment regimen and age (Table 5.6.2), an increasing risk for retinopathy was found for older individuals (above 50.5 years) on insulin therapy. These findings also suggested that older individuals on dietary treatment were less likely to have retinopathy when compared to younger individuals.

5.6.2 Poisson Multivariate Regression

A Poisson regression procedure was carried out for the development of a parsimonious model as a means of evaluating the modified proportional hazards model that was used in the main analysis. The parsimonious model that was generated from the Poisson regression revealed log-likelihood statistics and p-values that were identical to those of Cox's parsimonious model to the fourth decimal place.

Table 5.6.1 Tests of Interaction

Interaction Term	Events*	Log-likelihood Ratio	p-value for Log-likelihood Ratio
Hypertension X Fasting Blood Glucose	115	0.004	0.95
Age X Fasting Blood Glucose	115	0.008	0.93
Sex X Fasting Blood Glucose	115	0.000	0.99
Age X Hypertension	116	0.086	0.77
Sex X Hypertension	116	0.002	0.97
Age X Treatment Regimen	116	1.679	0.20
Sex X Treatment Regimen	116	0.460	0.50

* Number of patients with data used for the analysis of this interation

Table 5.6.2 Relative Risks for Age in the Different Treatment Regimens

	Age: Above population mean vs. Below population mean (Old vs. Young)	
TREATMENT	Relative Risk	95% Confidence Interval
Dietary Treatment Alone	0.24	0.02 to 2.76
Oral Hypoglycemic Therapy	1.59	0.59 to 4.30
Insulin Therapy	2.15	0.39 to 11.96

Table 5.6.3 Poisson Regression Parsimonious Model: Poisson Compared with Proportional Hazards Model

Variable	Representation	Number of subjects	Cox's Regression p-value	Poisson Regression p-value
Body Mass Index	5 unit intervals	114	0.05	0.05
Cholesterol	Baseline (below mean)	59	0.07	0.07
	Elevated (above mean)	55		
Treatment	Baseline (Diet)	38		
	Oral vs. Diet	68	0.08	0.08
	Insulin vs. Diet	13	0.03	0.03

Underlined p-values significant at alpha = 0.05

6.0 DISCUSSION

This study was conducted to examine risk factors for diabetic retinopathy in the cohort of Cree diabetics from Moosonee and Moose Factory, Ontario. To date, no published data exists that specifically examines risk factors for retinopathy in a North American Indian community north of South Dakota.

The primary outcome of interest in this study, diabetic retinopathy, was assessed over the past four years as part of a screening program for diabetic retinopathy in the western James Bay Cree. Risk factor data were collected through a chart review of patient files for both Moose Factory and Moosonee. The main risks of interest included potentially modifiable risk factors, such as: BMI, serum lipid levels, fasting blood glucose, glycosylated hemoglobin, and blood pressure.

Since the entire population of known diabetics in these two communities was included in this study, relative risks for retinopathy could be determined. A modified Cox's proportional hazards model was performed to arrive at these risk estimates. Following descriptive and univariate analyses, a parsimonious model was created from variables that were significantly associated with retinopathy on univariate assessment. All other covariates were subsequently re-examined from within this parsimonious model. Secondary analyses included a consideration of risk estimates generated by Poisson multiple regression. An 'a priori' examination of interaction terms was also performed as an exploratory part of the secondary analyses.

Multivariate results indicated that risk factors for diabetic retinopathy in the Cree of Moose Factory and Moosonee included body-mass index, serum cholesterol levels and insulin therapy. Both serum cholesterol and insulin treatment were positively associated with retinopathy. Body-mass index had an inverse association with retinopathy -- individuals with and elevated BMI were less likely to have disease.

In the ensuing sections, the main results of this study are briefly presented in summary form and discussed. Methodological issues are subsequently addressed and recommendations are made for future research.

6.1 BACKGROUND STATISTICS

6.1.1 Prevalence of Diabetes in Moose Factory and Moosonee

The crude diabetes prevalence estimate for Moosonee and Moose Factory was based upon potentially inaccurate population figures for Moosonee. This problem arose because the Regional Health Office did not have up-to-date census data for Moosonee. As a consequence, this community's population was approximated from Band Council estimates that placed the number of the Cree in Moosonee near 2,300. Using this figure, the prevalence of diabetes in this community was found to be lower than that in Moose Factory. This discrepancy may have been partially related to a higher proportion of non-natives in Moosonee, and/or less a complete diabetes registry in the Moosonee Medical Clinic.

For the James Bay Cree of Quebec, Brassard found the crude prevalence of diabetes to be 2.7% (95% confidence interval 2.4% - 3.0%).[29] In the present study, the crude diabetes prevalence was significantly higher in both communities. This discrepancy does not appear to be due to sampling differences since both studies identified subjects through physician-diagnosed registries that used World Health Organization diagnostic criteria.

Because of problems with the Moosonee population data, age-standardized prevalence estimates were only calculated for Moose Factory. In Moose Factory, the diabetic registry was up-to-date and age-distribution statistics were available. Direct age-

standardization demonstrated a prevalence estimate of 10.3% (95% CI 8.86% to 11.76%) for individuals over 15 years of age. In Brassard's study, the age-adjusted prevalence was 6.6% (95% CI 5.9% to 7.3%) for those over 20 years of age. Although Brassard used 20 years as a cut-off, the Quebec Cree's age-standardized measures were significantly lower than those for the Ontario Cree. In fact, if there was no differences in age cut-offs the age-adjusted prevalence measure for Moose Factory could have been even higher because of the low rate of diabetes found in the younger age groups.

The present study was not specifically intended to determine the prevalence of diabetes in the population under study. As a result, to equate the diabetes prevalence figures found in this investigation with Brassard's study of the Quebec Cree is not necessarily appropriate. First, the present study did not rigorously attempt to identify individuals with diabetes beyond those who were already known to the medical clinics. Second, no attempt was made to contact and arrange definitive diagnostic testing for those who had equivocal fasting blood sugars or glucose tolerance tests. Third, the incomplete identification of Moosonee subjects would have contributed to the likelihood of an poor estimation of the crude diabetes prevalence rate. Nonetheless, each of these limitations could have been expected to result in an underestimation of the true prevalence of diabetes in these two communities. For this reason these estimates are significant because they suggest that the prevalence of diabetes might well be markedly higher in the James Bay Cree than previously reported.

The higher diabetes prevalence in Moose Factory and Moosonee is possibly due to differences between the two populations and not simply one of research methodology. One possible explanation could be that inhabitants of Moose Factory and Moosonee are less isolated than their Quebec counterparts. Brassard's study showed a geographic gradient in the prevalence of diabetes such that more isolated communities were somewhat protected from this disease. (Isolation may protect natives from diabetes through preservation of

traditional livelihoods and diets.) Theoretically, the diabetes prevalence differences for Moose Factory and Moosonee could simply indicate that these communities are less isolated than those considered in Brassard's paper.

Two patients with insulin-dependent diabetes were identified during the course of this study, yielding a prevalence of 0.039% (95% CI 0.0046% to 0.14%). This 95% confidence interval approximates that of the Quebec Cree (0.01% to 0.10%).[29]

6.1.2 General Summary Data for Moose Factory and Moosonee Diabetics

The summary statistics for diabetics in Moose Factory and Moosonee only provide a brief overview of the state of diabetes in the two communities; nonetheless, it was interesting to note that so many more women were found to have diabetes than men, especially since women make up less than 50% of the total population of Moose Factory and Moosonee. This discrepancy might be partially a result of differences in life expectancy between sexes, it could also relate to other factors. For example, traditional hunting practices are still common-place for the Cree men of James Bay whereas lifestyle changes over the past few decades may have more dramatically affected women. Alternatively, women might be more willing to seek medical care and hence may be diagnosed with diabetes more frequently than men.

Another interesting statistic was the number of subjects on anti-hypertensive medication (66%). This finding could be explained either by a significant association between diabetes and hypertension, or by an over-prescription of these medications. Interestingly, the average serum creatinine and blood urea nitrogen levels for the entire cohort were within the normal range for individuals without diabetes--suggesting that primary hypertension and not diabetic renal failure is the likely mechanism for hypertension in these people.

Other summary data was presented in Table 5.1.2 for the entire cohort. Specifically, average values for a sampling of lab studies was presented. Interpretation of these summary statistics was not uncomplicated because the presented average lab values included data for many individuals that were taken at an arbitrary point in their life. To suggest that a collection of such potentially capricious measures would give a good representation of these values for the entire study population is suspect. This is one reason why efforts were made to identify a time period from which comparable lab values could be collected for the main analysis of this paper.

Notwithstanding this criticism, the full cohort's average serum creatinine, blood urea nitrogen, and serum cholesterol were within the normal non-diabetic range. As might be expected, hemoglobin A1C levels were significantly elevated for this cohort when compared to non-diabetic normal values.

6.1.3 Diabetic Screening Statistics

To date, 83% of subjects have had at least one ocular screening examination performed by the retinal specialists of the Moose Factory diabetic retinopathy screening program. Many patients have had multiple eye examinations. Some of those that have yet to be seen in the retina screening clinics have been evaluated by primary eye care providers during periodic ophthalmic and optometric visits to the region.

For the 12 and 18 month periods leading up to the last screening visit, 76% and 64% of all subjects, respectively, were screened by retina specialists. These rates of examination are excellent when compared to other Canadian populations. In Nova Scotia, for example, only 49% of diabetics were seen by an ophthalmologist in the three year period between 1987 and 1990.[25]

6.1.4 Comparison of Diabetics With and Without Eye Examinations

Comparisons were made between those who had received eye examinations and those that had not. The results of these univariate comparisons indicated that individuals who had not had ocular assessments were younger, had diabetes for a shorter duration, more likely to be from Moosonee, and more likely to have their disease controlled by diet. In general, those without eye examinations appeared to be at a less advanced stage of diabetes and, as a result, could be assumed to be at reduced risk for developing retinopathy. This is a fortuitous finding since it could suggest that the present screening program is targeting those individuals who are at greater risk for developing retinopathy.

6.1.5 Comparison of the Limited Cohort with those Excluded

The primary objective of this paper--to assess risk factors for diabetic retinopathy--was conducted on a carefully defined cohort of subjects, the 'limited' cohort. Only those with exposure data for a specific five year block, beginning one year after the diagnosis of diabetes, were included. These individuals also had to have had eye examinations.

The 'limited' cohort was chosen for the main analysis in an attempt to provide some standardization to the exposure data. It was hoped that by defining a more precise time period from which exposures could be recorded, a more meaningful measure of each variable would be used in the main analyses. One concern with this approach was its' exclusion of a number of individuals from the main analyses. (A more detailed discussion of the rationale for the use of the specific five-year period was presented in section 4.5.)

6.1.6 Types of Retinopathy

The final area of background statistics that were examined for this study focused on the three different types of retinopathy that were identified by the retina specialists. Proportions of these main clinical classes of retinopathy were as follows: no retinopathy

65.5%, background retinopathy 25.3%, macular edema 7.5%, and proliferative retinopathy 1.7%. Thirty-four percent had some evidence of retinopathy.

A cross-sectional study of the Hopi and Navajo Indians of Arizona found that 57% of these Indians had evidence of retinopathy.[64] It appears that the prevalence of retinopathy in the James Bay Cree is significantly less than in the Hopi and Navajo. In fact, the percentages of retinopathy presented above for the James Bay Cree are not from a cross-sectional assessment but from as screening program that was conducted over a period of four years. The true prevalence data for the three classes of retinopathy is possibly even lower than the proportions presented. At present, diabetic retinopathy prevalence data is not known for the James Bay Cree and cannot be derived from this study. As a result, rigorous comparisons of the proportions of retinopathy from the present study with other cross-sectional studies are not possible.

6.2 PRIMARY OBJECTIVE

A discussion of the primary results of this study follows. Specifically, significant univariate and multivariate relative risk estimates for retinopathy are considered in detail.

6.2.1 Univariate and Multivariate Associations with Retinopathy

Univariate relative risks for the development of diabetic retinopathy were determined for all independent variables. Significant associations included: duration of diabetes, body-mass index, hemoglobin A1C, fasting blood glucose, insulin therapy, and serum cholesterol. Body-mass index was protective when elevated. For the other five variables, an increased risk for the development of retinopathy was observed.

The next step in the main analysis involved re-assessing the relative risk of each

variable for diabetic retinopathy while controlling for the three variables in the parsimonious model. This multivariate procedure did not identify any significant variables except for those already in the parsimonious model. Insulin treatment and body mass index were both predictive of retinopathy at the 0.05 level. Serum cholesterol levels were predictive of retinopathy at the 0.056 level. Duration of diabetes, hemoglobin A1C, and fasting blood glucose were not significant predictors of retinopathy after adjusting for BMI, treatment status, and serum cholesterol levels.

6.2.2.1 Insulin Treatment Regimen

Individuals on insulin treatment were 4.71 times more likely to develop retinopathy than those on dietary treatment alone. This was the strongest association observed in this study. It is understandable that those on insulin were more likely to develop diabetic retinopathy. For type 2 diabetics, insulin therapy is typically an indication that an individual has had poor blood sugar control on oral hypoglycemics and, as such, it is also an indication of more advanced disease. Diabetic retinopathy would be expected to be more prevalent under these circumstances.

Brassard's work with the Quebec Cree also found a similar association between insulin therapy and microvascular complications. However, the relationship between treatment regimen and diabetic retinopathy was not paralleled in Lee's study involving Oklahoma Indians. Whereas Lee found a significant association with oral hypoglycemics and not insulin, West's earlier study of retinopathy in the same population found that insulin therapy was associated with diabetic retinopathy on multivariate analysis.[26,27] A comparable finding was also noted in the WESDR III, which found an association between insulin treatment and retinopathy .[35]

6.2.2.2 Body-mass Index

Elevated body-mass index was inversely associated with retinopathy. A relative risk of 0.64 was found for those with a five-unit higher BMI (BMI range 21.6 to 52.5 kg/m^2). This suggests that a 36% reduction in risk was observed with a five unit increase in BMI. Other studies have observed this same association. The WESDR III and West's study in the Oklahoma Indians both demonstrated an inverse relationship between BMI and diabetic retinopathy.[26, 35]

An explanation for this association may lie in the severity of each individual's underlying diabetes. Theoretically, obese individuals may have a milder degree of diabetes that is related, primarily, to insulin resistance.[26,35] Those with a milder degree of diabetes would also be expected to be less prone to the development of retinopathy.

Interestingly, the BMI values for the limited cohort indicate that this population is quite obese--assuming a BMI over 27 indicates obesity. In fact, the cohort may be so obese that the interpretation of the relative risk for BMI is difficult. Certainly, the increased risk of retinopathy for individuals with a lower BMI does not necessarily apply that those of normal BMI but to less obese individuals, since almost all subjects were obese.

6.2.2.3 Serum Cholesterol

In this study, increased serum cholesterol levels did approach significance on multivariate assessment at the 0.05 level ($p = 0.056$). Individuals with a serum cholesterol level greater than the limited cohort's average (5.2 mmol/L) were almost 2.5 times as likely to have retinopathy when compared to those with lower levels.

Serum cholesterol is a medically modifiable exposure that plays a role in the pathogenesis of many vascular diseases. In light of the clinical importance of this variable, the arbitrary nature of a 0.05 significance level is highlighted. The role that cholesterol may

play in the development of diabetic retinopathy cannot be dismissed on the basis of a 0.056 p-value. In fact, this variable should be considered very carefully by ophthalmologists, endocrinologists and family physicians who care for Cree people with diabetes. Unlike the other significant variables, body-mass index and treatment regimen, cholesterol levels are more easily modifiable by changes in diet and the judicious use medications. Serum cholesterol is therefore a clinically important variable, eventhough it demonstrated borderline statistical significance in this analysis.

The magnitude of the clinical importance of this variable is highlighted if the relationship between cholesterol and retinopathy is assumed to be causal. In situations where a causal link between an exposure and an outcome is known, the public health impact of modifying the exposure can be described in terms of population attributable risk (PAR). This measure can be interpreted as the fraction of cases occurring in the population that could be avoided by eliminating the risk factor. The PAR takes into account both the magnitude of risk and the number of individuals exposed. For serum cholesterol, the population attributable risk percent for an elevated serum cholesterol was 40%, indicating that amongst all diabetics, 40 % of the cases of retinopathy were attributable to elevated serum cholesterol levels.[57] Similarly, 40% of all cases of retinopathy could be avoided if the population's serum cholesterol levels could be kept below 5.2 mmol/L.

For this study, cholesterol was represented in a dichotomous form. It is possible that larger risk estimates may have been observed with greater contrasts in exposure, such as the highest quartile versus the lowest quartile. However, a post priori examination of cholesterol in quartiles did not demonstrate significance on multivariate analysis--with BMI and treatment regimen in the model. A relative risk of 2.87 was found for the comparison of the highest and lowest quartiles, but this result was not statistically significant (95% CI 0.79 to 10.46). The limited number of subjects available for this quartile analysis resulted

in several categories having few subjects, and therefore, poor statistical power to demonstrate associations.

Table 6.1 Quartile Representation of Serum Cholesterol

Cholesterol Level (mmol/L)	Events (Retinopathy)	Number at risk	Multivariate Relative Risk†	95% Confidence Interval
< 4.4 mmol/L	3	29	baseline	
4.5 to 5.1 mmol/L	3	28	1.02	0.20 - 5.17
5.2 to 5.9 mmol/L	6	26	2.14	0.53 - 8.59
>6.0 mmol/L	13	33	2.87	0.79 - 10.46
Total Number	25	116		

† relative risks are based on a comparison with the referent baseline quartile

As shown in Table 6.1, the multivariate relative risk estimates for cholesterol and retinopathy showed an increase in magnitude over baseline for each quartile--supporting the likelihood of a dose-response. When the categorical representation of cholesterol was then tested for trend, using non-factored data, a significant trend was found for this variable's association with retinopathy ($p = 0.047$). Although the underlying cause of diabetic retinopathy is diabetes, serum cholesterol may contribute as a causal factor to the development of retinopathy. This may be particularly true in the present study's limited cohort of younger people with diabetes.

The specific criteria that give evidence for a causal relationship between an exposure and an outcome include: strength of association, biologic credibility, consistency with other investigations, a dose-response relationship, and temporal plausibility.[65] Using the information presented above, the possibility of a causal link between serum cholesterol and retinopathy can be considered by examining each of these five criteria.

First, on multivariate analysis this study demonstrates a reasonably strong association between serum cholesterol and retinopathy (RR = 2.38).

Second, a biologic mechanism for the deleterious effect of elevated serum cholesterol on the systemic vasculature is well known. It is reasonable to postulate that elevated serum cholesterol levels similarly affects the retinal microvasculature--increasing the likelihood of an individual developing retinopathy.

Third, the association between serum cholesterol and diabetic retinopathy is not well defined in the literature. Pima and Cree Indian studies indicate that there appears to be some evidence of a reproducible association between retinopathy and serum lipid levels in North American natives. Elevated total serum cholesterol was found to be a risk for proliferative retinopathy in the Pima Indians[44], and Brassard's examination of the Quebec Cree found a significant association between serum triglycerides and diabetic microvascular disease.[50] However, West and Lee's studies of Oklahoma natives did not demonstrate any association between serum cholesterol and retinopathy.[26,27] These varied results suggest that the exact nature of the cholesterol-retinopathy relationship is still in question for the North American Indian population.

Fourth, the test for trend presented above indicates that a dose-response does exist for serum cholesterol and diabetic retinopathy.

Finally, the present study presents evidence for a temporal relationship (exposure preceeding outcome) between serum cholesterol and retinopathy. For the limited cohort, serum cholesterol levels were determined from lab values taken in the early years following an individual's diagnosis of diabetes (years 2-6). Lab values were always drawn before the assessment of retinopathy, and for the most part, subjects were rarely found to have retinopathy in the first few years after their diagnoses. This suggests that serum cholesterol levels were likely drawn prior to the development of retinopathy. Furthermore, since

almost all patients with retinopathy were asymptomatic, i.e. did not have vision loss, it is unlikely that retinopathy would have altered serum cholesterol levels as a consequence of the disease process. If vision loss was associated with retinopathy in this study population, it could have affected the general activity levels or diet of these individuals to the point that their systemic cholesterol levels could also have become elevated.

The preceding section suggests a possible causal association between serum cholesterol levels and diabetic retinopathy in the Cree. However, a clear answer to the question of an association between serum cholesterol and diabetic retinopathy for all North American natives is not possible. North American Indians are not a genetically or culturally homogeneous people, the literature suggests that different diabetic populations appear to be affected differently by this exposure. For this reason, it seems reasonable to suggest that serum cholesterol levels should be part of future trials and studies considering risk factors for retinopathy in native populations.

Notwithstanding this need for future research into these questions, if one considers this study and Brassard's together, the Canadian Cree diabetic population seems to demonstrate evidence of an association between serum lipid levels and microvascular disease. These results suggests that routine testing of serum lipid levels should be part of the management of Cree people with diabetes. If one accepts a causal link between serum cholesterol and retinopathy for the diabetic population of Moose Factory and Moosonee, then, as the PAR% statistic indicates, lowering the serum cholesterol levels for these individuals could be expected to significantly reduce the prevalence of diabetic retinopathy for those at risk.

6.2.2.4 Other Variables

An interesting finding of this analysis was the absence of duration of diabetes, fasting blood glucose and hemoglobin A1C as predictors of retinopathy. These associations

have been well described in the literature (Section 2.3, 2.4), yet, for this cohort these variables did not demonstrate significance on multivariate assessment. This may be due in part to the relatively short duration of diabetes for the 'limited' cohort. It may also suggest that earlier in the course of diabetes, these well-known risk factors are not necessarily the main predictors of retinopathy in the Cree population. Alternatively, since fasting blood glucose and hemoglobin A1C measurements were determined at a single point in time--within the first few years following the diagnosis of diabetes--these variables may not be representative of long-term blood glucose control. In fact, measures of these variables taken within the first few years following the diagnosis of diabetes may be more normal than measurements taken later in the course of this disease.

The absence of an association between duration of diabetes and retinopathy may also have been due to strong correlations between duration of diabetes and the other significant variables--namely BMI, serum cholesterol and treatment status (Tables 5.3.1 and 5.3.3). Thus, the apparent effect of duration in the univariate analysis is explained by these other factors in the multivariate model. A similar effect may have also influenced the relationship between hemoglobin A1C and retinopathy, since glycosylated hemoglobin was strongly associated with serum cholesterol and treatment status.

6.2.2.5 Screening for Diabetic Retinopathy

The results of the present study are especially important for individuals concerned with screening for diabetic retinopathy. Periodic screening is essential for all known diabetics but may be more important for diabetics with certain risk profiles.

Since this study focused more on diabetics with a shorter duration of diabetes, the risks identified in this analysis could direct screening efforts for individuals who are in the

earlier stages of diabetes. For example, individuals with normal ocular assessments at the time of diagnosis might be followed more frequently if elevated serum cholesterol levels, lower BMIs, or insulin therapy were noted in their first few years of diabetes.

6.3 SECONDARY ANALYSES

6.3.1 Poisson Regression

Poisson regression was performed as a validation of the modified Cox's model that was used for the main analysis. This was done to determine if both multivariate techniques were comparable and to substantiate the use of a modified Cox's model in a setting where typical regression diagnostics do not necessarily apply.

Results of the Poisson regression revealed that the same three variables were significant on stepwise variable selection at the 0.10 inclusion level as were found on the proportional hazards model. In fact, identical log-likelihood statistics and p-values were generated in the development of the Poisson parsimonious model. It was interesting to find such similar results for both these multivariate models because the Poisson model's underlying rare disease assumption was violated by the high prevalence of retinopathy in the limited cohort.

6.3.2 Interaction

'A priori' interaction terms were assessed using the Cox's parsimonious model. Models containing the three significant multivariate exposures and the first order terms for the interaction were extended to test the significance of the interaction term. No significant interactions were found in the course of these exploratory analyses. In fact, all the interaction terms demonstrated very low log-likelihood ratios, some of which approached '0'. A trend towards significance was noted for 'age and treatment regimen'. The risk

ratios for these terms suggested that for older individuals, over 50.5 years, the risk of diabetic retinopathy was increased if they were on insulin and decreased if they were on dietary treatment alone--compared to those less than 50.5 years.

6.4 METHODOLOGY

6.4.1 Cohort Identification

One of the main strengths of this study was the assessment of diabetic retinopathy in a previously unstudied cohort of native Canadians. All individuals with diabetes in Moosonee and Moose Factory that could be identified through their respective outpatient medical clinic databases comprised the cohort. Since there was only one medical clinic in each community, there was little risk of missing subjects who were receiving their medical care elsewhere.

Unfortunately, the identification of subjects was also limited by the accuracy of these clinic databases. This was less of a problem in Moose Factory where the actual patient charts are flagged at the time of diabetes diagnosis--allowing charts with these marks to be easily identified. In Moosonee, the patient charts were not marked for identification of those with diabetes. As a result, it was not possible to identify diabetics that were not in the computer registry. This did pose a problem since the Moosonee computer diabetes database had not been updated in the past one-to-two years. A full review of all clinic charts would have been required to find these individuals. For this reason, a number of new diabetics were undoubtably missed from Moosonee; however, considering that subjects in Moosonee were less likely to have had ocular assessments or complete exposure data (Table 5.1.2), many of the unidentified patients from Moosonee

database would likely not have met inclusion criteria for the main analysis. (Of patients from Moosonee, only 46% (22/48) had data for the three variables in the parsimonious model--compared to 86% (94/109) for Moose Factory patients. See Table 5.5.2.)

In addition to potential problems with the identification of Moosonee subjects, there is also a segment of the population with diabetes who have either subclinical diabetes or are not under direct medical supervision. These individuals would not have been registered in the clinics and could not have be identified, let alone assessed, in the context of this study.

Despite the possibility that significant numbers of eligible diabetics were missed during the data collection process, the number of individuals included in this study would have been difficult to increase. As of the last data collection visit to James Bay, all known people with diabetes were identified and included. Had the investigators wanted to increase the size of the cohort, one option would have been to hand search all the clinic charts in both communities for evidence of undiagnosed or unidentified diabetics. Another option would have been to collect data for people with diabetes in the other James Bay communities. Unfortunately, such undertakings were not possible because of transportation costs, time constraints, and person-power limitations.

Even if visits to other communities were possible, it is not likely that there would have been large numbers of individuals with complete data for the risks considered in this study. In Moosonee, a large town with easy access to physicians and hospital resources, much exposure data was missing from patients' charts. It would be expected that for the more remote communities even less exposure data would have been available. The efficiency of data extraction trips to the smaller outposts would have been very low in light of these concerns.

To properly maximize the number of study subjects, and consequently the power, of any future study assessing retinopathy in Western James Bay, a prospective design would have to be considered. Unless exposure information is recorded carefully and

completely at the time of patient enrollment and follow-up, the problem of missing data will always be present, especially if a chart review study like the present one is considered.

6.4.2 Outcome Assessment

The choice of diabetic retinopathy as the primary outcome for the present study was influenced by the retrospective nature of this project. Since detailed retinal assessments or photographs were not available from patient charts, the precise extent and grade of each subject's retinopathy was not consistently determinable--only three levels of retinopathy were reliably recorded. Because of this, the presence or absence of retinopathy was the most rigorous categorization possible. Nonetheless, problems with this categorization were encountered during data collection.

Misclassification bias was the main concern. During the course of the early screening visits to Moose Factory, participating physicians did not know that their grading of diabetic retinopathy was to be used as an outcome for a research project such as this. For this reason, the recording of the more minor changes indicative of retinopathy may have been omitted from their assessments. This mostly would have affected individuals with very early changes of retinopathy i.e. a single microaneurysm or blot hemorrhage. Those with these minor retinal changes may have been diagnosed as having no retinopathy in the period before the specific objectives of this study were defined. Misclassification of this nature would have been non-differential, since these errors would have unlikely been related to one or more of the exposures of interest.

As an alternative to the use of retinopathy as the main outcome of interest, macular edema or proliferative disease could have been considered as outcomes. Another option would have been to grade retinopathy along a spectrum, conceptualizing it as a continuous

variable. Unfortunately, the low prevalence of macular edema and proliferative retinopathy, and the even less precise recording of degree of retinopathy did not make such analyses possible.

6.4.3 Missing Data

As with most retrospective cohort studies, problems arose with the completeness and accuracy of chart information for the exposures of interest in this project. As a result, a significant number of patients were excluded from the multivariate data analyses because information on certain covariates was not available. Specifically, lipid profiles and fasting blood sugar tests had not been performed on all subjects.

Attempts were made to locate missing data from hospital charts at the time of data collection. As well, specific missing values were diligently sought by the medical staff in Moose Factory after the final data collection team had returned to Kingston--all efforts were made to ensure data collection was as complete as possible.

Unfortunately, despite attempts to collect missing values, the amount of missing data undoubtably affected the power of this study to identify all significant exposures for the development of retinopathy. The power calculation, presented in section 4.8, was based on an estimation of 118 subjects; however, for the multivariate model, the number of subjects that had complete data was often closer to 115. Furthermore, the power calculation over-estimated the 'p_o' values (p_o = probability of an outcome in an unexposed individual). Instead of p_o probabilities in the range of 0.50, as estimated from Lee's study of the Oklahoma Indians[27], the probabilities for this study were closer to 0.25. The lower p_o values were probably a consequence of the shorter duration of diabetes for the 'limited' cohort members. As a result, this study did not have the power to show a significant

difference between exposure groups at a relative risk of 1.5 (sections 4.8.1 and 4.8.2). The relative risk would have to have been increased to 2.0 for the power to have exceeded 80%.

Options that could have been considered for increasing the power of this study, without increasing the relative risk beyond 1.5, were discussed in section 6.4.1 and focused on increasing the number of research subjects.

6.4.4 Selection Bias

The issue of missing data also created possible problems in terms of selection bias. Of the 283 subjects identified in both communities, 42 of these people had not had eye examinations. Of the remaining 241, 84 did not have exposure data for the specific time period of interest. This left only 157 individuals for the main analysis.

A comparison of the 157 individuals in the limited cohort and the 84 who were excluded was performed. Significant differences between these groups were found for almost all variables compared. Patients in the limited cohort were younger, had diabetes for a shorter duration and were more commonly on dietary treatment regimens. They also had elevated body-mass indices and lower hemoglobin A1C levels.

These differences between groups can be partially explained by the availability of the more advanced liver function and fasting blood glucose tests. In Moose Factory, both of these tests have only been performed since the late 1980s. As a result, individuals with diabetes diagnosed in the 1970s, or earlier, did not have this exposure data for their early diabetic years. This is likely the reason why people in the limited cohort were younger and had diabetes for a shorter interval than those who were not. Moreover, if subjects who had diabetes for longer were more likely to be on insulin, the limited cohort would also be expected to have had a significantly different distribution of their treatment regimens. Differences in the presence of retinopathy were probably also related to differences in the duration of diabetes for the two cohorts.

The inclusion of a larger proportion of Moose Factory diabetics in the limited cohort may have been a result of the increased completeness of laboratory studies for these individuals. It may have been easier for physicians or nurses to obtain laboratory tests for patients who attended the Moose Factory clinic because a laboratory is located in the same building.

A second concern surrounding the issue of selection bias was briefly considered earlier. In section 6.1.4 it was noted that subjects in Moosonee were less likely to have had ocular assessments. An explanation for this could be that, as with laboratory testing, the Moose Factory cohort had easier access to the screening ophthalmology clinics, which were all conducted in Moose Factory. If this is indeed the case, future screening efforts might be most appropriately aimed at diabetics in Moosonee and the other outlying communities. Future multivariate analyses should also be considered to identify factors associated with missed ocular assessments. Such research would allow more accurate determinations of where screening efforts should be directed.

6.4.5 Exposures Assessed

The variables evaluated in the present study were single measures taken from a specific five-year period in each subject's life. As such, the values of these variables do not represent long-term exposure status but are proxy measures for chronic exposure. Due the the relatively infrequent testing of most laboratory parameters in the cohort under study, there were no other feasable options that would have provided a reproducible and accurate estimate of chronic exposure status. Therefore, a decision was made to standardize the period from which this data would be accepted.

The choice of exposures included in the present study was based on expected risk factors and confounders for diabetic retinopathy; however, because of the retrospective nature of this study it was not possible to assess exposures that were not routinely recorded

in the patients' outpatient and inpatient charts. As a result, the covariates evaluated were not an exhaustive assembly of possible risk factors, confounders, and effect modifiers for diabetic retinopathy. No cultural or environmental variables that could have been important exposures were available. Specifically, factors such as socio-economic status, physical activity level, alcohol consumption, diet, and measures of traditional lifestyle were not addressed. Such variables have been implicated as risk factors that may play a role in the development of diabetic retinopathy.[66] No studies to date have made any attempts to measure these potentially important risk factors.

Despite this concern, it is likely that some of the aforementioned cultural and environmental risk factors would have been mediated by clinical measures that were included in this study. For example, levels of physicial activity would likely be partially represented by BMI and serum cholesterol levels--making some of these extra exposures less essential for inclusion.

6.4.6 Design Strengths

Most of the methodological limitations of this study have been reviewed in the preceding sections. The strengths of this project have yet to be discussed in light of the other literature that has examined similar questions. Briefly, this study provides insight into a common complication of a prevalent disease in a unique population. It also considers potential risk factors for diabetic retinopathy in a carefully defined and standardized manner--only data from years one-to-six following the diagnosis of diabetes was considered for the main analyses. Despite the uncertainty surrounding the actual onset of type 2 diabetes, no other retrospective or cross-sectional study has attempted to use this rigorous a defining interval for risk factors of interest.

In comparison, Lee's and West's studies used a cross-sectional determination of

risk factors and, as a result, exposure data was not taken from equivalent points in the diabetic disease process for each participant.[26,27] The same problems were found in Brassard's study of the James Bay Cree. His study looked at cross-sectional data and retrospective data from the 30 month interval preceding each individual's assessment by the research unit.

Another positive aspect of this study was the determination of relative risks for the development of retinopathy. The availability of a relatively complete cohort of individuals with diabetes allowed this possibility. Both Oklahoma studies and Brassard's paper used logistic regression to evaluate multivariate associations in situations where the rare disease assumption did not hold and odds ratios could not be expected to approximate relative risk.[26,27,50]

A final strength of this study was the manner in which exposure and outcome associations were somewhat temporally isolated. Compared with cross-sectional designs, exposure assessments for the present study were all performed prior to each subject's ocular examination. The possibility still existed that retinopathy may have been present at the time of exposure assessment; yet, for individuals who had examinations within their first few years of diabetes--when most lab values were taken--retinopathy was rarely found.

Despite the strengths of the present study, the prospective studies that examined risks for retinopathy were methodologically stronger. The Pima and Wisconsin cohorts were able to assess risk factors from comparable times in each participant's disease process. In addition, these studies had ongoing follow-up which allowed the use of unmodified Cox's proportional hazard regression techniques. True incidence rates were also calculable from these studies.

6.4.7 Generalizability

The results presented in this paper provide data on a very specific population of people with diabetes--Cree Indians from Moose Factory and Moosonee. These individuals are only a small sample of all the Cree in the region and, as such, there may be differences between this cohort and Cree from other communities in the James Bay region. While Moose Factory and Moosonee are isolated, they do have large populations and a rail link from the south. Consequently, there is more opportunity for these individuals to make non-native lifestyle choices than for individuals residing in more isolated northern areas.

A further problem arises if one attempts to generalize these results to other non-Cree native groups. The diversity, both genetic and environmental, between native peoples does not ensure that any of these results could be reproducible in even neighbouring Algonquin tribes such as the Ojibwa of north-western Ontario. It follows that extending these results to other Canadian or American native peoples would be inappropriate. Nonetheless, if taken in the context of the other studies of diabetic retinopathy in North American natives, these results do help to broaden our understanding of risk factors for retinopathy in indigenous peoples of our continent. Specifically, this paper highlights the possibility that BMI, insulin therapy, and serum cholesterol may affect the development of diabetic retinopathy. Although this study suggests that there may be a role for risk factor modification in the prevention of diabetic retinopathy, judicious use of this study's results to enhance retinal screening programs through the identification of high risk individuals is perhaps the most appropriate use of this information.

6.5 FUTURE DIRECTIONS

Further research into diabetic retinopathy in Canadian native populations should probably take the form of prospective cohort studies. Protocols that parallel the WESDR

and the Pima studies are the most appropriate ways to generate incidence data and to address risk factors for retinopathy and other diabetic complications. If such studies are initiated, every effort must be made to include as complete a cohort of the population under consideration as possible.

Future studies must also have extensive local involvement from their inception to ensure that native cultural concerns are respected and addressed. A unique consideration is the need to define what research questions should be asked. For example, although the research presented in this thesis was conducted in careful consultation with the Omuskegowuk Band Council, it did not address underlying cultural issues such as the First-Nation belief that diabetes is related to their loss of traditional ways of life--at the hands of western cultural influences. Instead, the questions that were asked came directly from the perspective and tradition of western medicine. This is not to say scientific methodology is unimportant but in the setting of population-based research it cannot overlook the fact that two different cultures are interacting in the processes of medical research.

To address these concerns, future studies should consider including band members and native health-care workers in the design and conceptualization stages. Efforts should also be made to include questionnaires that measure variables such as 'degree of traditional lifestyle maintained'. Ultimately, the integration of cultural concerns and scientific methodology will more likely produce research that is meaningful to all participants.

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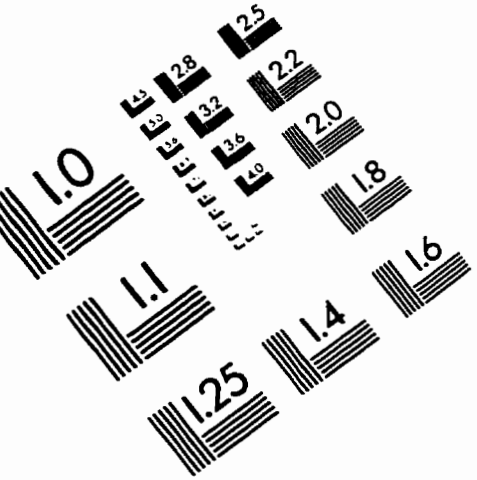
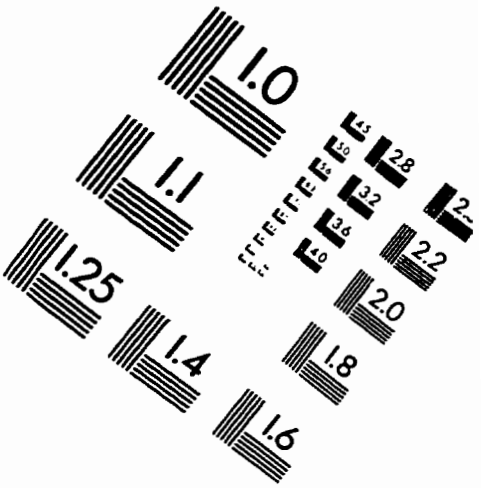
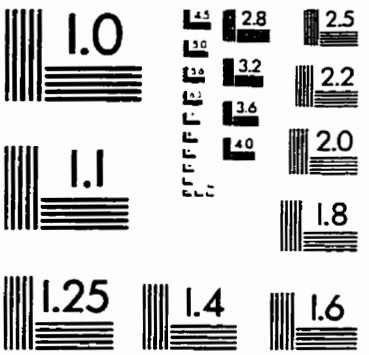
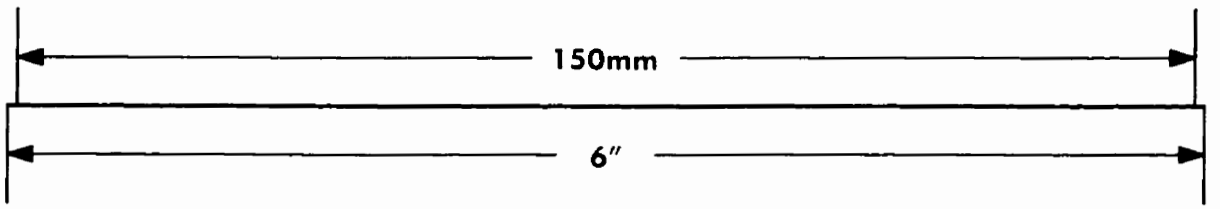
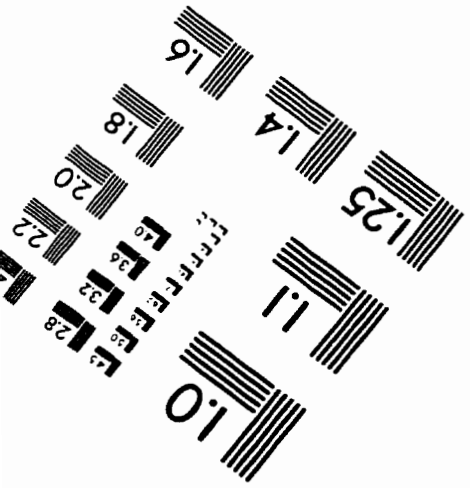
IMAGE EVALUATION TEST TARGET (QA-3)

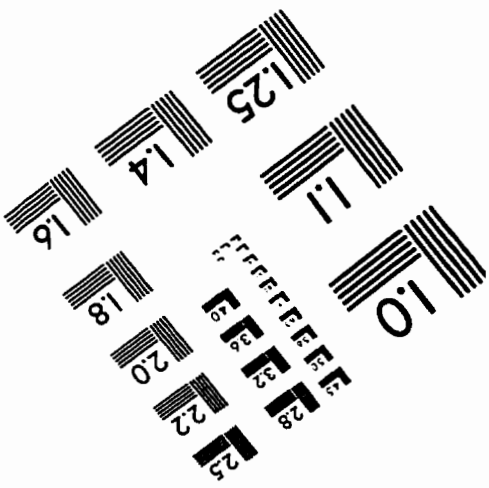












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