

NON-TRAUMATIC FRACTURES IN INDIVIDUALS WITH DIABETES

NON-TRAUMATIC FRACTURES IN INDIVIDUALS WITH DIABETES

by

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ABSTRACT

Background: Previous studies have found that diabetes is associated with increased risk of fragility fracture; however, the risk of non-traumatic fracture (of any bone) specific to individuals with diabetes across the Canadian population has not been studied. Similarly, the best way to identify which individuals with diabetes are at elevated risk remains unknown.

Objectives: This thesis aimed to define the risk of non-traumatic fracture among Canadians with diabetes, and to identify risk factors.

Methods: Ten years of data from the Canadian Multicenter Osteoporosis study was explored. Logistic regression models were used to study factors associated with a history of previous non-traumatic fracture at study baseline. Cox proportional hazards models were used to explore time-to-incident-fracture during the 10 years of study.

Results: Women and men ≥ 50 years in the CaMos database were included in the analyses (n=7753). This included 508 individuals with non-insulin dependent diabetes mellitus and 98 with insulin-dependent diabetes mellitus. Mean age was 67 (± 9) years and 72% were female. Individuals with diabetes were found to be more likely to have a history of fragility fracture than non-diabetic CaMos participants (odds ratio [OR] =1.21, 95% confidence interval [CI] 1.00,1.46; p=0.04), but were less likely to be treated with bisphosphonate therapy at any point over the 10 year study (OR: 0.58; 95% CI 0.46,0.75; p<0.001). Macrovascular disease in the form of stroke/TIA and hypertension was found to be associated with previous non-traumatic fracture amongst the diabetic population

(OR: 1.51; 95% CI 1.20,1.91; $p<0.001$; and, OR: 1.16; 95% CI 1.04,1.29; $p=0.01$ respectively).

Conclusions: A treatment care gap exists amongst diabetics in Canada. Individuals with diabetes are at increased risk of non-traumatic fracture, but are less likely to be treated with bisphosphonate therapy. Clinicians can use specific fracture risk factors, including a history of cerebrovascular disease, hypertension and insulin use, to identify which diabetics are at highest risk and target interventions accordingly.

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CHAPTER 1 –BACKGROUND

1.1 BACKGROUND

1.11 Diabetes in Canada

Diabetes is a common condition and rates around the world are increasing at an alarming pace. The increase is thought to be mostly secondary to the increasing incidence of obesity around the world, as 90% of type 2 diabetes is caused by excess weight (Houssain 2007). Rates are expected to reach pandemic levels by 2030 when the global incidence of the disease is predicted to hit 438 million (Houssain 2007, CDA 2011). In Canada, 9 million people currently have diabetes or prediabetes; of these, 90% have type 2 diabetes and 10% have type 1 (CDA). Type 1 diabetes occurs when an individual experiences an absolute deficiency of insulin; usually the result of pancreatic beta-cell failure. Most commonly this occurs in childhood and is thought to be the result of an autoimmune process, possibly triggered by viral infection in individuals who are genetically susceptible (Hobner 2010). This is different from type 2 diabetes where the causes are multifactorial, including both genetic and environmental influences, and result in significant peripheral insulin resistance and beta-cell dysfunction (Scheen 2003). Unlike individuals with type 1 diabetes who immediately require insulin therapy, most people with type 2 diabetes initiate therapy with oral medications to maximize the effects of their own endogenous insulin. However, with time beta-cell function declines and some individuals with type 2 diabetes do require insulin therapy (CDA 2008).

Diabetes (both type 1 and type 2) is associated with multiple complications which lead to increased morbidity and mortality in this population. Complications are often divided into macrovascular (complications arising from larger arteries; including stroke, heart disease and peripheral vascular disease) and microvascular (complications arising from small arteries; including retinopathy, neuropathy, and nephropathy). Screening and treatment guidelines are in place so these complications can be identified and managed in a consistent and systematic fashion by all treating clinicians. Risk factor modification including lipid, blood pressure and glucose management are actively pursued at most patient encounters. The most recent Canadian guidelines recommend screening for microvascular and macrovascular complications on an annual basis or as indicated (CDA 2008). The elevated fracture risk associated with diabetes is a relatively newly identified complication of diabetes of which many clinicians are still unaware. There are no Canadian diabetic screening or treatment guidelines currently in place that address fracture risk.

1.12 Osteoporosis in Canada

Osteoporosis, from Greek for “porous bone”, is “a skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture” (Anonymous, 1993). In 1992 the World Health Organization (WHO) defined osteoporosis as “a measured value of bone mineral more than 2.5 standard deviations below the mean for young healthy adult women at any site” (Wylie, 2010); however, more recently the focus has shifted from measuring and treating low bone mineral density (BMD) values to assessing absolute fracture risk and treating to prevent fragility fractures (Papaioannou, 2010). Globally, one in 3 women and one in 12 men are currently

affected by osteoporosis (Keen 2003). In Canada, 21% of women and 5% of men over the age of 50 have osteoporosis (Berger 2010) and these numbers are expected to rise as the population ages (Hanley 1996). Current Canadian guidelines recommend assessing fracture risk factors in all women and men over the age of 50 in order to identify individuals at high risk of having a non-traumatic fracture (Papaioannou, 2010). Despite the high prevalence of osteoporosis in Canada, a “care gap” is present. Half of Canadian women and more than half of Canadian men, with osteoporotic fractures are not put on treatment for their osteoporosis (Fraser 2011, Papaioannou 2008).

1.13 The Impact of Non-Traumatic Fractures

Fragility fractures, associated with osteoporosis, are fractures that occur with minimal trauma, such as a fall from standing height or less (Kanis 2001, Bessette 2008). Multiple different definitions of fragility fracture have been used over time by different authors. Therefore, to be clear, the term non-traumatic fracture will be used in this thesis to denote fractures caused without significant trauma that, in an individual without compromised bone integrity, would not have occurred. Classically these have involved fractures of the proximal femur (hip), vertebrae (spine), radius (wrist), and proximal humerus (shoulder). Non-traumatic fractures at multiple other sites also occur more frequently in individuals with osteoporosis, but are less important in terms of morbidity (WHO 1998). Of the classic non-traumatic fractures associated with osteoporosis, hip fracture is considered the most important as it creates the greatest morbidity and economic burdens as well as increased mortality. 41% of elderly patients require nursing facility placement after a hip fracture and 26% die within the first year post-fracture (Wiktorowicz 2001, Bentler 2009). Both hip and vertebral fractures have been found to

be associated with increased mortality rates (Ioannidis 2009, Kado 1999). Quality of life declines significantly in patients affected by osteoporotic fractures with on-going pain, disability, increased depression, decreased mobility, decreased cognitive abilities, and decreased ability to perform activities of daily living (Bentler 2009, Papaioannou 2009, Adachi 2001, Johnell 2006). In Canada the direct medical costs of osteoporosis, mostly related to acute fracture care and rehabilitation post-fracture, are estimated to be 1.9 billion dollars per year (Osteoporosis Canada 2011). In the United States the costs are between 17 to 20 billion dollars per year (Beaker, 2010). However, the actual costs are thought to be much greater after incorporating lost wages, care giver burden, and the cost of nursing home care. The costs associated with treating hip fracture patients have been found to be 3 times greater than similar patients without a fracture (Haentjens 2005). On a global level, it is predicted that by 2050, 6 million individuals will fracture their hip each year (Keen 2003) leading to significant morbidity, mortality and strain on health care systems around the world.

1.14 Estimating Fracture Risk

Bone mineral density (BMD) is used by many clinicians in the diagnosis and therapeutic management considerations for osteoporosis. However, although BMD is an important risk factor for fracture risk, it does not accurately predict all non-traumatic fractures (Leslie 2003). In fact, most osteoporotic fractures occur in individuals with BMD values above the osteoporotic range (Cranney 2007, Schuit 2004, Stone 2003). Therefore, there has been a change in focus in recent years, from BMD scores alone, to the use of fracture prediction tools to more accurately identify individuals in need of interventions to prevent fragility fractures. The new Osteoporosis Canada guidelines, published in November 2010, suggest tailoring therapy to individuals with

elevated fracture risk identified with fracture prediction tools (Papioannou 2010). In Canada, the updated tool of the Canadian Association of Radiologists and Osteoporosis Canada (CAROC) and the World Health Organization's (WHO) Canada-specific Fracture Risk Assessment tool (FRAX) are available to predict patient specific fracture risk (Leslie 2011, Fraser 2011, Leslie in press). These tools use BMD scores in concert with different clinical risk factors, which have been found to be independently associated with fracture risk, to more accurately predict 10-year fracture risk. The clinical risk factors include: age, gender, body mass index (BMI), parental history of hip fracture, current cigarette smoking, alcohol intake, rheumatoid arthritis, glucocorticoid use, previous fragility fracture and secondary causes of osteoporosis. Diabetes is included as a clinical risk factor for fracture under "secondary causes" in these tools, but neither tool has been validated in a diabetes-specific population.

1.15 Strategies to Prevent Fracture in Individuals at Elevated Risk

Multiple effective, evidence-based, treatment modalities have been identified to decrease the incidence of fragility fracture in individuals found to be at elevated fracture risk; making the ability to identify individuals at-risk of utmost importance. Lifestyle interventions including cessation of smoking, moderation in alcohol and caffeine intake, and regular weight-bearing exercise are encouraged (Hernandez 1991, Wallace 2000, Brown 2002, Papaioannou 2010). Optimizing calcium and vitamin D intake have become first-line interventions as combined vitamin D and calcium supplementation has been shown to have a beneficial effect on BMD, and to reduce falls and fracture risk in some individuals (Cranney 2007). A variety of bone-specific medications with fracture reduction efficacy are now available; these include: bisphosphonates, teriparatide, estrogen, selective estrogen receptor modulators (SERMs), calcitonin and

denosumab. Bisphosphonates, the most commonly used bone-specific therapy currently, decrease vertebral and nonvertebral fracture risk by up to 50%, and are cost-effective for treatment of osteoporosis in Canada (Goeree 2006, Cranney 2002). The specific effect of known fracture-reduction interventions in the diabetic population have not been studied.

1.15 Scope of thesis

This thesis will first review the literature to-date regarding fracture risk among individuals with diabetes and possible risk factors for non-traumatic fracture in these individuals. The methodologic challenges associated with the study and the study methods and results will then be described in detail. This will be followed by a discussion of the findings and thesis conclusions.

CHAPTER 2 –DIABETES AND FRACTURE RISK: REVIEW OF THE LITERATURE AND RESEARCH QUESTIONS

2.1 REVIEW OF THE LITERATURE

2.11 Increased Fracture Risk in Diabetes

In recent years multiple studies, including cross-sectional cohort, case-control, and prospective longitudinal cohort studies, have been performed showing that diabetes (both type 1 and type 2) are associated with an increased risk of non-traumatic fracture. In the Nord-Trondelag Health Survey (1999) the relative risk of hip fracture in women with type 1 diabetes was elevated at 6.9 (95% CI 2.2,21.6)(Forsen 1999) compared to the non-diabetic population. In women with type 2 diabetes for more than 5 years the relative risk was 1.8 (95% CI 1.1,2.9). This risk was further increased if the woman was on insulin (RR: 2.2, 95% CI 1.0,4.9). Men over the age of 75 with type 2 diabetes for less than 5 years were also at increased risk of hip fracture (RR: 2.1; 95% CI 1.1,4.2).

Two meta-analyses on the risk of fractures in the diabetic population were published in 2007 with risk estimates, somewhat different due to the studies included. Janghorbani et. al included 11 cohort and 1 case-control study in their type 2 diabetes analysis, and 5 cohort and 1 case-control study in their analysis of type 1 diabetes. They reported an increased risk of hip fracture in women and men with type 2 diabetes (RR: 1.7; 95% CI 1.3,2.2) and with type 1 diabetes (RR: 6.3; 95% CI 2.6,15.1)(Janghorbani 2007). Vestergaard reported similar results with an elevated risk of hip fracture in patients with type 2 diabetes (RR: 1.38; 95% CI 1.25,1.53) and type 1 diabetes (RR: 6.94; 95% CI 3.25,14.78). The Vestergaard paper included 2

case-control and 6 cohort studies (1 cross-sectional and 5 longitudinal) in the type 2 diabetes analysis, and 1 case-control and 4 longitudinal cohort studies in the type 1 diabetes analysis.

In other studies type 1 diabetes has also been found to be associated with increased risk of fractures of the wrist (Vestergaard 2005), foot (Seely 1996), vertebrae (Vestergaard 2005), non-vertebral fractures (Ahmed 2006) and “any fracture” (Vestergaard 2005). Increased fracture risk, at sites other than “the hip”, has also been reported in type 2 diabetes. These include an increased risk of non-vertebral fractures (Schwartz 2001, De Leifde I 2005, Ahmed 2006), vertebral fractures (Nicodemus 2001, Vestergaard 2005, Bonds 2006, Schwartz 2009), “any fracture” (Nicodemus 2001, Taylor 2004, Vestergaard 2005, Bonds 2006), fractures of the proximal humerus (Ivers 2001), and wrist fractures (Vestergaard 2005, de Leifde II 2005).

Despite multiple studies in other countries, in Canada there has been very little peer-reviewed published literature on the association between fracture risk and diabetes. In the only Canada-wide study performed to-date, Hanley et al. examined prevalent vertebral deformities, as measured by spinal radiographs, and found no significant increase in individuals with type 1 diabetes (OR: 1.24; 95% CI 0.68,2.51) or type 2 diabetes (OR: 0.91; 0.67,1.25)(Hanley 2003). Clinical vertebral fractures or fractures at other sites were not evaluated, and therefore there is no information currently on these fractures in the diabetic population in Canada. A handful of provincially based studies have been performed. In Ontario a study of hip fracture risk in men and women with diabetes found increased fracture risk in men (HR: 1.18; 95%CI 1.12,1.24) and women (HR: 1.11; 95% CI 1.08,1.15)(Lipscombe 2007). This study was limited to the province of Ontario, did not look at fracture sites other than the hip, and did not differentiate between type 1 and type 2 diabetics. In Quebec, the population of patients undergoing solid-organ transplantation have been studied and those with pre-transplant diabetes were found to be at

increased risk (after controlling for glucocorticoid use and other potential confounding variables), compared to those without diabetes, of fracture after discharge from hospital post-transplant (adjusted OR: 1.94; 95% CI: 1.5,2.6)(Rakel 2007). In Manitoba, a population-based study by Leslie et al. showed that individuals with long-term (>5 years) diabetes was associated with an increase in osteoporotic fractures (RR: 1.15; 95% CI 1.09,1.22) and hip fractures (RR: 1.40; 95% CI 1.28,1.53)(Leslie 2007). In addition, Leslie has studied the Canadian aboriginal population and found diabetes to be a risk factor for fracture in this population as well (Leslie 2006). These two studies (by Leslie) were performed using administrative databases and therefore are limited in that they were unable to control for possible confounding variables such as peripheral neuropathy and falls.

2.12 Pathophysiology of Increased Fracture Risk in Diabetes

Although the pathophysiology has not been definitively determined, there is a substantial body of evidence suggesting the cause of increased fracture risk in the diabetic population is different from typical primary (post-menopausal) osteoporosis. Similarly, the causes of impaired bone strength are likely different in type 1 vs. type 2 diabetes.

Type 1 diabetes is associated with decreased bone formation (rather than increased bone resorption which is typical of primary osteoporosis) caused by a shift in bone marrow stem cell development away from differentiation into osteoblasts and towards adipocyte differentiation instead (McCabe 2007). The absolute insulin deficiency which defines type 1 diabetes also plays a role in decreased bone quality as insulin, through the actions of insulin-like growth factor 1 (IGF-1), has important anabolic effects on bone. Other causes of bone fragility specific to type 1

diabetes may include: decreased pancreatic amylin secretion, impaired regulation of adipokines, vitamin D deficiency and autoimmune dysfunction (Hofbauer 2007, Reid 2008).

In contrast, type 2 diabetics seem to have a decreased risk of fracture early in their disease possibly secondary to their larger body mass index (BMI) and the increased BMD associated with that, as well as their hyperinsulinemic state (Leslie 2007, Merlotti 2010). However, with time and disease duration fracture risk increases (Leslie 2007, de Liefde II 2005). Factors common to impaired bone strength in type 1 and type 2 diabetes include hyperglycemia and the formation of advanced glycation endproducts (AGE). Hyperglycemia increases osteoclast activity while impairing the action of osteoblasts, and the associated glucosuria can cause hypercalciuria leading to a negative calcium balance (Merlotti 2010). AGE interfere with type 1 collagen cross-links in bone, leading to decreased bone quality (Saito 2010). Type 2 diabetics may also be put on a thiazolidinedione (TZD) for their hyperglycemia. These PPAR- γ agonists decrease osteoblast differentiation and increase bone loss, and have been found in trials to increase fracture risk (Kahn 2008, McDonough 2008).

2.13 Risk Factors for Fracture in Diabetes

Due to the different mechanisms causing bone fragility in diabetics (vs. primary osteoporosis) as discussed in section 2.12, we cannot assume that risk factors for fracture in these two populations are necessarily the same. BMD for instance is an important risk factor used in fracture prediction in post-menopausal osteoporosis. However, multiple studies have found individuals with type 2 diabetes to be at increased fracture risk despite having significantly higher BMD levels than non-diabetic patients (de Liefde II 2005, Vestergaard 2007); highlighting possible discrepancies in risk factors between these two populations.

Traditional clinical fracture risk factors (CRF) currently used in fracture risk assessment tools like FRAX and CAROC have been found in studies to be independently associated with increased fracture risk (De Laet 2005, Kanis 2004, Kanis 2005). These are discussed in section 1.14. Currently there is only one report in the literature examining some of these traditional risk factors specifically in a diabetic population. In 2008 Melton et al. reported on a diabetic population living in Rochester Minnesota and found age, BMI, prior fracture, secondary osteoporosis and corticosteroid use to be risk factors for future fracture in this population (Melton 2008).

Other studies have focused on factors specific to diabetes, rather than traditional CRF. Increased BMI and centripetal obesity, which are commonly seen in type 2 diabetes, have been found in some studies to have a protective effect, increasing BMD and decreasing the risk of fracture (Kanazawa 2008, Yamaguchi 2009). Risk of fracture has been found to increase with the duration of diabetes (deLiefde II 2005, Leslie 2007), possibly due to the increased incidence of micro- and macrovascular complications that occur with time. These complications include: retinopathy, neuropathy, peripheral vascular disease, stroke and myocardial infarction, all of which have been linked to increased fracture risk (Lipscomb 2007, Patel 2008, Ivers 2001). It is possible that the associations between these diabetic complications and fracture risk are mediated by an increased fall risk seen in severe disease (Patel 2008). Hyperglycemia has been found in multiple studies to be associated with increased fracture risk (Ivers 2001, Merlotti 2010). Insulin use has also been associated with increased fracture risk in some studies (Ivers 2001), possibly representing a marker of more severe, long-standing disease in type 2 diabetes. Insulin also predisposes patients to hypoglycemic episodes and therefore increased fall risk. However, other studies have found a decreased fracture risk in diabetics using insulin (Vestergaard 2005),

perhaps relating to the fact that insulin has an important anabolic effect on bone. Likewise, insulin therapy has been found to be associated with enhanced bone formation (McCabe 2007) and the hyperinsulinemia associated with early type 2 diabetes may even be protective against fracture (Yamaguchi 2009). Sulfonylurea medications and metformin have been associated with a decreased fracture risk (Vestergaard 2005) whereas rosiglitazone has been found to be associated with a 2-fold increase in fractures (Kahn 2008).

2.14 Unanswered Questions

The only Canada-wide study to-date looking at elevated fracture risk in diabetics studied X-ray vertebral deformities only (Hanely 2003). No study has looked at non-traumatic clinical fractures of all types (both vertebral and non-vertebral, including fractures of the hip, forearm, ribs, pelvis, and elsewhere) in the diabetic population in Canada. Similarly, there are very few studies within the diabetic population examining risk factors which differentiate, who is at increased fracture risk, amongst diabetics. No study to-date has looked at diabetes-specific risk factors for fracture within the Canadian diabetic population. Similarly, there are no studies looking at osteoporosis treatment rates amongst the diabetic population. Given the osteoporosis treatment care gap that has been identified in the general population, we hypothesize that an even greater care gap exists within the diabetic population.

This thesis aims to address these unanswered questions; to define fracture risk in the Canadian diabetic population, to identify diabetes-specific clinical risk factors that increase fracture risk and to examine treatment rates.

2.2 RESEARCH QUESTIONS

- What is the risk of non-traumatic fracture in Canadians with insulin-dependent and non-insulin dependent diabetes?
- What risk factors can be used to identify Canadians with diabetes at increased risk of non-traumatic fracture?
- Are Canadians with diabetes on appropriate osteoporosis therapies?

Specific Objectives:

- A) To define the risk of any non-traumatic fracture in individuals with insulin-dependent diabetes compared to individuals without diabetes, in individuals with non-insulin dependent diabetes, and in any individual with diabetes (insulin and non-insulin dependent)
- B) To identify which traditional fracture risk factors predict risk of fracture in Canadians with diabetes
- C) To identify what diabetes-specific risk factors predict risk of fracture in Canadians with diabetes
- D) To determine if individuals with diabetes in Canada are at increased risk of falling compared to individuals without diabetes
- E) To determine if individuals with diabetes are more/less likely to be on treatment with a bisphosphonate than individuals without diabetes

2.3 METHODOLOGICAL CHALLENGES ADDRESSED IN THE THESIS

2.3.1 Accuracy of the diagnosis of type 1 diabetes

The original aim of this thesis was to separately analyze fracture amongst Canadians with type 1 and type 2 diabetes. Traditionally it has been very difficult for large database studies to differentiate between type 1 and type 2 diabetes as the International Classification of Disease (ICD-9) code (250) used to identify diabetes does not differentiate between type 1 and type 2. As such, most studies assume that the majority of the diabetics studied have type 2 diabetes given the increased prevalence of type 2 diabetes in the population (Lipscombe 2007, Leslie 2007). The baseline Canadian Multicenter Osteoporosis Study (CaMos) questionnaire does differentiate between type 1 and type 2 diabetes (a strength of this study), however the accuracy of this differentiation is uncertain as it is dependent on patient self-report. To test whether the CaMos questionnaire accurately identified individuals with type 1 diabetes an analysis was performed looking at the self-reported age of diagnosis of “type 1 diabetes” in those who identified themselves as type 1 diabetics. In the past, diabetes was often divided into “insulin-dependent diabetes” and “insulin-independent” diabetes; terms that are not generally used in the medical community today (Abduelkarem 2004). However, this often leads to confusion amongst people with diabetes who obtained their diabetes education and diagnosis when these terms were commonplace. During the CaMos baseline questionnaire participants were asked “has your doctor ever told you that you have any of the following conditions: (multiple conditions listed), diabetes: 1= insulin dependent, 2= insulin independent”. Type 1 diabetes usually occurs in children and young adults. Therefore, the self-reported age of onset of “diabetes 1= insulin dependent” was examined to see if the CaMos questionnaire accurately identified individuals

with type 1 diabetes or if instead it identified individuals with insulin-dependent diabetes (which would include those with type 1 diabetes as well as certain individuals with type 2 diabetes with inadequate pancreatic function).

2.32 Confounding

In order to avoid a confounded result, leading to an erroneous association between diabetes and fracture risk, statistical models were developed which incorporated controlling for variables which have previously been identified as fracture risk factors.

2.33 Missing data

As is common in studies of large databases, missing values create a problem by potentially biasing results to individuals with full datasets, who may be significantly different from subjects with limited information or cessation of study participation. To deal with missing data in the CaMos database multiple imputation (Rubin 1989) was used (using 5 imputations) for variables with significant missing case numbers.

CHAPTER 3 –METHODS

3.1 CaMos

The Canadian Multicenter Osteoporosis Study (CaMos) is an on-going population-based cohort study looking at osteoporosis and fracture risk in community dwelling Canadians. Participants were unaware of their osteoporosis status at study baseline. Baseline questionnaires were completed in 1995-1997. The institutional review boards of all sites participating in CaMos approved the study and informed consent was obtained from all participants. The study has been described in detail elsewhere (Kreiger, 1999), but areas relevant to this study are summarized below. Data from years 0 through 10 were used for this thesis. All women and men aged 50 years or older were included in the analyses. Approval from CaMos investigators was obtained to proceed with this thesis.

3.11 Study Participants

Participants were recruited from within 50-kilometers of one of 9 study centers across Canada (St. John's, Halifax, Quebec City, Toronto, Hamilton, Kingston, Saskatoon, Calgary and Vancouver). 9,423 individuals (6,539 females and 2,884 males) aged 25 years and older, representing an age-stratified-, sex-, and region-specific sample, were identified from lists of random telephone numbers over an 18 month period.

3.12 Data Collection

An extensive interviewer-administered questionnaire was performed at baseline, and at years 3, 5 and 10 of the study. At baseline, years 5 and 10, lateral lumbar and thoracic spine X-

rays, and bone mineral density (BMD) testing were performed. BMD was also repeated at year 3, for women 40-60 years old at baseline. At years 1,2,4,6,7,8 and 9, a two-page questionnaire was mailed to participants asking about hospitalizations and fractures within the past year and current use of prescription bone-related medications. All participants who experienced a fracture received a follow-up phone call to enquire about the circumstances surrounding the fracture including: date, fracture site, circumstances leading to fracture, and medical treatment. In addition, consent was obtained to allow contact with the treating physician or hospital and verification of the radiology report. All participant medications were documented in detail during the interviewer-administered questionnaires.

3.13 Bone Mineral Density

BMD of the hip and lumbar spine (L1-L4) were measured by dual-energy X-ray absorptiometry (DXA) using Hologic QDR 1000, 2000, 4500 or Lunar DPX machines. Densitometers were calibrated daily, and quality assurance was performed following a standard daily and weekly schedule. Initially, cross-calibration of the machines was performed at the nine centers using a European Spine Phantom. After this, the Bone Fide phantom was performed at baseline and in the year of every examination. Reports indicating bone density (g/cm^2), and T-scores were sent to each participant, a physician named by the participant or both depending on the centre (Kingwell 2010).

3.14 Fractures

All clinically recognized non-traumatic fractures were included in the analysis. Any fracture associated with trauma or described as a fall from more than standing height was

excluded. At baseline, previous fractures were obtained by self-report. Fractures that occurred after study entry were reported by patients and subsequently confirmed by medical or radiographic reports.

3.2 Statistical Analysis

All analyses were restricted to CaMos participants ≥ 50 years. Baseline characteristics of the CaMos participants were described using mean (\pm standard deviation) for continuous variables and count (percentage) for nominal variables. A summary table of pre-planned analyses is presented in table 1.

Factors associated with a history of previous non-traumatic fracture at CaMos study baseline were examined with a logistic regression model, using an enter method. Variables included in the model were: age, gender, femoral neck T-score, insulin dependent diabetes mellitus (IDDM), non-insulin dependent diabetes mellitus (NIDDM), rheumatoid arthritis, and family history of osteoporosis. Age was divided into 10-year categories (50-59, 60-69, 70-79, 80-89, and ≥ 90). Age 50-59 was used as the reference category in the analyses. Other known predictive variables, such as corticosteroid use, were not included in the analyses due to large amounts of missing data or small numbers. IDDM and NIDDM were chosen as the subject of primary interest to this study. All other independent variables included in the model were selected because they are risk factors that have previously been identified as having important associations with fracture risk. The regression model was also run after combining IDDM with NIDDM for a “total diabetic” term. To test model goodness-of-fit the Hosmer and Lemeshow Chi-square test was performed. Multiple imputation was performed for missing data in order to assess the robustness of the model. The results of the model before and after multiple imputation

are reported. A logistic regression model was also used to examine bisphosphonate use. “Ever bisphosphonate use” (ie. patient reported being on a bisphosphonate at any time point during the 10 years studied) was examined with the variables listed above and also history of non-traumatic fracture at baseline, as an additional variable.

Factors associated with incident fractures (new fracture during the 10 year observation period) were assessed using a Cox Proportional Hazards Model. Time to first incident non-traumatic fracture was evaluated, with model variables including: age, gender, rheumatoid arthritis, family history of osteoporosis, femoral neck T-score, history of previous non-traumatic fracture, and diabetes status (IDDM or NIDDM). Analyses were performed before and after multiple imputation and then repeated looking at the combined group of IDDM and NIDDM.

The diabetic subgroup of the CaMos population was then examined using a logistic regression model to identify diabetes-specific risk factors for previous non-traumatic fracture. Micro and macrovascular complications of diabetes have been proposed in the past as possible causes of the increased fracture risk in diabetics, therefore these were examined. Variables included: kidney disease (microvascular disease), history of myocardial infarction, stroke or TIA, hypertension, gender, age, femoral neck t-score, rheumatoid arthritis, and family history of osteoporosis. A Cox Proportional Hazards Model then examined time to first incident non-traumatic fracture in the diabetic population using the same variables.

Risk of falls was examined using a logistic regression model with the term “ever fall” used as the outcome variable. Subjects were included as having an “ever fall” if they were identified as having had at least one fall in CaMos questionnaires at years 0, 3, 5 or 10 (falls were not assessed during other years of the study). Variables in the model were the same as

those used in the models listed above. All calculations were performed using IBM SPSS version 19 (Ireland).

CHAPTER 4 –RESULTS

4.1 Baseline characteristics

Participant selection is detailed in figure 1. Characteristics of the CaMos population over 50 years (n=7753) and of participants with insulin-dependent diabetes (n=98) and non-insulin-dependent diabetes (n=508) are described in table 2. Table 3 shows the outcome variables present in each group.

Examination of the self-reported age of diagnosis of type 1 diabetes revealed that only 10 individuals (9.6% of self-reported insulin dependent diabetics) were under the age of 30 years when they were diagnosed with diabetes. This implies that this group consists mostly of type 2 diabetics who are insulin dependent (relative insulin deficiency) rather than type 1 diabetics (absolute insulin deficiency). Therefore this thesis will refer to ‘insulin dependent’ diabetes and “non-insulin dependent” diabetes rather than type 1 and type 2 diabetes.

As seen in table 2, baseline characteristics were similar between all groups. The diabetic groups had higher BMD values than the general CaMos population. This finding is similar to other studies which have shown higher BMD values in type 2 diabetics likely on the basis of the elevated BMI which is a risk factor for developing type 2 diabetes (Hofbauer 2007, Vestergaard 2007). This difference in BMI was also evident in the CaMos population (BMI of 27 vs. 29 in diabetic participants). Despite having superior BMD values, individuals with diabetes were more likely to have had a non-traumatic fracture at baseline (39% of IDDM and 29% of NIDDM compared to 27% of the general CaMos population). IDDM reported a longer duration of diabetes, 15 compared to 10 years, which is to be expected as type 2 diabetes progresses over time leading to more need for insulin use later in the disease process.

4.2 Risk of Fracture (Objective A)

Individuals with diabetes were more likely to have a history of non-traumatic fracture than non-diabetic CaMos participants (OR:1.57; 95% CI 1.24,2.00; $p<0.001$). This risk was elevated in both individuals with insulin-dependent diabetes and those with non-insulin-dependent diabetes (OR: 2.43; 95% CI 1.39,4.23; $p=0.002$; OR: 1.44; 95% CI 1.11,1.87; $p=0.006$ respectively). Other factors that were found to be associated with a history of non-traumatic fracture at study baseline (all with $p<0.004$) were: femoral neck T-score (OR: 0.76), rheumatoid arthritis (OR: 1.44), age 70-79 years (OR1.41) and family history of osteoporosis (OR: 1.35). For the above logistic regression analysis, SPSS automatically excludes cases from the analysis when one data value is missing, a large portion (49.4%) of the study population was missing at least one value. Therefore, multiple imputation was performed for the variables: family history of osteoporosis, rheumatoid arthritis and femoral neck T-score (which were the variables with a high number of missing data points). This increased the number of patients included in the regression model from 4771 to 7741. The results remained similar, diabetes was associated with a history of non-traumatic fracture (OR: 1.21; 95% CI 1.00,1.46, $p=0.045$). IDDM was still associated with a history of previous fracture (OR: 1.82; 95% CI 1.20,2.77; $p=0.005$), however NIDDM was no longer significantly associated with previous fracture (OR: 1.11; 95% CI 0.90,1.36; $p=0.320$) (table 4). The Hosmer and Lemeshow Chi-square test was not significant in this model, indicating good fit. In this model, other factors associated with a history of non-traumatic fracture (all with $p<0.05$) were: increased age, female gender, femoral neck T-score, family history of osteoporosis, and rheumatoid arthritis.

A cox proportional hazard model was used to examine time-to-first-non-traumatic fracture over 10 years of CaMos study. The variables, femoral neck T-score, rheumatoid

arthritis, and family history of osteoporosis, were again corrected using multiple imputation. A total of 1189 individuals experienced a new non-traumatic fracture over the 10 year study period. There was no difference found in fracture incidence in the IDDM (HR: 1.028; 95% CI 0.66, 1.61; p=0.898) or the NIDDM (HR: 1.03; 95% CI 0.80, 1.32; p=0.817) groups. Similarly, the hazard ratio was not significant when the subjects with diabetes were pooled together (HR: 0.86; 95% CI 0.64, 1.16; p=0.333). The hazard ratios remained not significant when time-to-first hip fracture, and time-to-first vertebral fracture, were used as the outcome variable.

4.3 Diabetes-Specific Risk Factors (Objectives B and C)

Prior to multiple imputation, within the diabetic population in CaMos, there were 335 individuals to examine. History of a stroke or TIA (macrovascular disease) was found to be associated with a history of non-traumatic fracture (OR: 1.65; 95% CI 1.22,2.23; p=0.001). Family history of osteoporosis, age greater than 70 years, rheumatoid arthritis, and low femoral neck T-score were also more likely to be found in the group of diabetics that had a history of fracture. After multiple imputation the number of diabetics included in the analysis went up to 597. History of cerebrovascular disease (in the form of a stroke or TIA) was still found to be associated with fracture amongst diabetics (OR: 1.51; 95% CI 1.20,1.91; p=0.001) but hypertension was also identified as being associated with fracture amongst diabetics (OR: 1.16; 95% CI 1.04,1.29; p=0.010). An interaction term for stroke and hypertension was not significant. Other risk factors found to be important within the diabetic population (table 5) were: rheumatoid arthritis, family history of osteoporosis, older age, female gender and BMD. Duration of diabetes was not significant when added as a variable. When time-to-fracture was

examined within the diabetic population, age was the only variable found to be significantly associated with incident fracture (table 6).

4.4 Risk of Falls (Objective D)

Questions relating to patient falls were found in CaMos questionnaires at years 0, 3, 5 and 10, but not other years. In years 0 and 3 subjects were asked about falls in the past week or past month, whereas at years 5 and 10 they were asked about falls in the past 12 months. To explore the differences in fall incidence between participants with and without diabetes, an outcome variable of “ever fall” was created. If an individual reported a fall in any of the fall questions then they were considered to have had an “ever fall” for the purposes of this hypothesis-generating analysis. Diabetes status, hypertension, cerebrovascular disease and gender were used as co-variates because of biologic plausibility to be associated with fall risk. Logistic regression with “ever fall” as the outcome (n=7698) did not support diabetes as being associated with falls (OR: 1.13; 95% CI 0.95,1.35; p=0.163)(table 7).

4.5 Treatment (Objective E)

Individuals with diabetes were less likely to be on bisphosphonate therapy compared to other CaMos subjects (OR: 0.68; 95% CI 0.50, 0.93; p=0.016). After multiple imputation was performed for the variables: rheumatoid arthritis, family history of osteoporosis and femoral neck BMD; the relationship strengthened (OR: 0.58; 95% CI 0.46,0.75; p<0.001). Other variables associated with decreased likelihood of bisphosphonate use were older age (OR: 0.99; 95% CI 0.98,1.0; p=0.001) and increased femoral neck T-score (OR: 0.40; 95% CI 0.36,0.44; p<0.001). Variables associated with increased bisphosphonate use included: rheumatoid arthritis

(OR: 1.28; 95% CI 1.04, 1.58; p=0.072), family history of osteoporosis (OR 1.25; 95% CI 1.07,1.45; p=0.004), female gender (OR: 3.04; 95% CI 2.62,3.51; p<0.001), and history of non-traumatic fracture (OR: 1.20; 95% CI 1.06,1.36; p=0.003). When diabetes was broken down into insulin-dependent and non-insulin-dependent and bisphosphonate use was examined, the results were not statistically significant prior to multiple imputation. However, after multiple imputation for variables listed above, non-insulin-dependent diabetes was found to be associated with decreased use of bisphosphonates (OR: 0.59; 95% CI 0.45,0.78, p<0.001), as was insulin-dependent diabetes (OR: 0.53; 95% CI 0.29,0.95; p=0.034). All logistic regression models (before and after multiple imputation) were found to provide good fit, with the Hosmer and Lemeshow Chi-square test not being significant.

CHAPTER 5 -DISCUSSION

This analysis found that Canadians with insulin-dependent diabetes are 82% more likely to have had a non-traumatic fracture, and Canadians with non-insulin-dependent diabetes are 11% more likely, than other Canadians over 50 years of age without a diagnosis of diabetes. This increased risk did not appear to be secondary to an increased risk of falls in those with diabetes. Within the diabetic population traditional fracture risk factors of rheumatoid arthritis, family history of osteoporosis and decreased BMD were associated with increased fracture risk; but also macrovascular complications, in the form of stroke or TIA, increased fracture risk by 58%. Hypertension, a macrovascular risk factor and not a commonly thought of fracture risk factor, was also found to increase fracture risk amongst diabetics by 20%. Despite the increased risk for non-traumatic fracture in those with diabetes, Canadian diabetics in CaMos were 42% less likely than non-diabetics to be treated with a bisphosphonate over the 10 year study period; indicating a significant care-gap in skeletal care amongst Canadians with diabetes.

The finding of increased history of non-traumatic fractures amongst diabetics in CaMos is in-keeping with previous literature showing this population to be at elevated fracture risk. The most recent meta-analyses indicate an increased relative risk for hip fracture in type 2 diabetics of 1.4 to 1.7 and in type 1 diabetics of 6.3 to 6.9 (Janghorbani 2007, Vestergaard 2007). In Canada, information about fracture risk in those with diabetes is less abundant. The only Canada-wide population based study to date was also performed in the CaMos population. This study however, looked only at prevalent vertebral fractures by radiograph and showed no increased risk in type 1 or type 2 diabetes (Hanley 2003). By analyzing the age-of-onset of “type 1

diabetes” in the CaMos population for this study, serious doubt was cast on the accuracy of the “type 1 diabetes” definition within the CaMos study; this group more likely represents type 2 diabetics who have become insulin dependent. Our study is the first to show an increase in clinical non-traumatic fractures, at any body site, in individuals with diabetes at a national level. These findings support previous, smaller province-wide studies, showing increased risk of hip fracture as well as osteoporotic fractures in type 2 diabetics (Lipscombe 2007, Leslie 2007).

The initial plan for the current study was to examine the differences between type 1 and type 2 diabetes, unfortunately, due to limitations of the CaMos database; this was not able to be done. However, the results (which examine insulin dependent diabetes and non-insulin dependent diabetes) are still relevant and informative. This is the first study to look at fracture risk differences amongst insulin dependent and non-insulin dependent diabetics across Canada. We found risk to be much higher in the (presumed type 2) diabetics on insulin, indicating that insulin dependence is an important risk factor for fracture in diabetics. This finding is in keeping with studies done in other countries showing insulin use further increases the risk of fragility fractures in those with diabetes, perhaps by acting as a marker of disease severity (Schwartz 2001, Forsen 1999, Ivers 2001).

Falls are not uncommon in the diabetic population (Schwartz 2008). Particularly in the insulin-dependent population this makes sense given the increased risk of hypoglycemia, as well as visual impairment (from diabetic retinopathy), orthostatic hypotension (from autonomic neuropathy) and peripheral neuropathy, all of which contribute to fall risk. Falls are an obvious and well-known contributor to fracture risk, and many authors have suggested the increased

fracture risk in diabetics is therefore explained by an increased likelihood of falling (Mayne 2010, Shwartz 2004). This may be true; however, we did not find an increased fall risk in CaMos participants with diabetes, despite an increased risk of fragility fracture, suggesting that other factors (perhaps in addition to falls) are at play here. Our falls analysis is limited by the availability of data which is only present for short periods of the 10 year CaMos study (at years 0, 3, 5 and 10) and by the method of self-reporting of falls which is of unknown accuracy. However, in the questions used in CaMos 35% of participants reported falling which is similar to the reported fall rate of 29% in elderly Canadian community dwelling individuals (O'Loughlin 1992), suggesting the CaMos questions did capture falls with some accuracy. Another confounding factor, which increases fracture risk in diabetic patients, is the use of thiazolidinediones for glycemic control (Vestergaard 2009, Kahn 2008). Thiazolidinedione use was therefore examined, and no one in the CaMos database was on one of these medications at study baseline.

Traditional fracture risk factors, such as those used in the FRAX and CAROC risk assessment tools, have been studied only to a limited degree within the diabetic population. Given the differences in fracture pathophysiology between diabetics and non-diabetics (see section 2.12), it cannot be assumed that fracture risk associated with traditional risk factors can be extrapolated to the diabetic population. A single study currently exists examining some traditional fracture risk factors in individuals with diabetes (Melton 2008). This study identified age, BMI, prior fracture, secondary osteoporosis and corticosteroid use to be associated with increased fracture risk in type 2 diabetics in Rochester Minnesota. Our study expands the list of traditional risk factors to include rheumatoid arthritis, family history of osteoporosis and

decreased BMD, as risk factors within the diabetic population that are associated with increased risk of non-traumatic fracture. We further examined diabetes-specific risk factors and found diabetics with cerebrovascular disease or hypertension to be at increased risk of non-traumatic fracture. Cerebrovascular disease (stroke, TIA) is known to be associated with fragility fractures in the general population (Ramnemark 1998). Immobilization and vitamin D deficiency often lead to decreased BMD in these individuals (Smith 2011), and residual problems with balance and dizziness pre-dispose to falls (Lamb 2003). To our knowledge, the only study to-date finding stroke as a risk factor for fracture specifically in the diabetic population is an Ontario-based study which found increased hip fracture risk in type 2 diabetics with a history of previous stroke (Lipscomb 2007). Our study expands stroke as a risk factor in diabetics for any non-traumatic fracture, not just hip. Hypertension is not widely recognized as a fracture risk factor. However, recent studies have identified an association between high blood pressure and bone fragility. A population-based study from Denmark found increased fracture risk (in a non-diabetic population) following a diagnosis of hypertension (Vestergaard 2009). This increased risk was found to be independent of stroke or myocardial infarction and independent of drug effects. In other studies, multiple different hypertension medications have been found to decrease fracture risk, supporting a link between blood pressure elevation and risk of fracture (Rejnmark 2006). Ours seems to be the second study showing a direct link between hypertension and fracture risk, and the first study to show this link in the diabetic population. Other studies have shown an association between hypertension and the surrogate outcome of increased BMD loss (Cappuccio 1999). This association may be mediated by increased urinary calcium losses in hypertensive individuals (Strazzullo 1991, McCarron 1980). Our study adds important information to the literature, arming clinicians with the knowledge that previous stroke/TIA and hypertension

further increase the risk of fracture in diabetic patients (facts that were previously not known). This knowledge can be an important tool to help practitioners differentiate risk in their diabetic patients and hence appropriately focus preventative strategies.

We found that, despite having increased rates of non-traumatic fractures, individuals with diabetes were less likely to receive treatment with a bisphosphonate than other CaMos participants. This care-gap has not been identified in the diabetic population previously. Within the general population however, it is well known that a large care gap exists with many patients not being diagnosed or treated for their osteoporosis. This care-gap has been documented both in Canada and internationally (Papaioannou 2004, Giangregorio 2006). Within the CaMos population there have been reports of a care-gap in men and women with fragility fractures; approximately half of women experiencing a new fragility fracture were found to not be treated with a bone-specific medication (Fraser 2011) and over 90% of men were untreated (Papaioannou 2008). Considering osteoporosis treatment rates within the CaMos population are so low, our findings of an even larger care-gap amongst those with diabetes within CaMos suggests a dire situation for these patients. An osteoporosis care-gap has not been reported in the diabetic population previously, and therefore there are no accepted theories as to why it exists above the level of the baseline care-gap in the general population. One possibility may be the higher BMD values typically found in individuals with type 2 diabetes. Traditionally, most clinicians used BMD scores to diagnose and make treatment decisions around osteoporosis. This bias is reflected in past osteoporosis treatment guidelines (Brown 2002). Although newer guidelines focus more on fracture risk assessment, and less on BMD alone, many clinicians still rely heavily on BMD when making treatment decisions. It is therefore possible that the normal or

elevated BMD values that are typically seen in type 2 diabetics (likely the result of higher BMIs in this population) make clinicians less likely to suspect osteoporosis. This highlights the need for education and knowledge dissemination to diabetic practitioners about the link between diabetes and fracture.

This study has several strengths including the large population-based sample, inclusion of both men and women, detailed fracture data, and the ability to differentiate between insulin dependent and non-insulin dependent diabetes. To our knowledge, this is the first Canada wide study to show increased fracture rates in the diabetic population and the first study that highlights the fracture treatment care-gap in diabetics. It is also the first study to show hypertension and cerebrovascular disease to be fracture risk factors in individuals with diabetes. There are however several limitations to this study. The inaccuracy of type 1 diabetes identification made it impossible for us to study differences between type 1 and type 2 diabetics. All the CaMos questionnaires depended on patient reporting (and therefore are subject to patient recall bias and misunderstanding), therefore the incidence of certain classically underdiagnosed conditions (such as hyperglycemia and hypertension) is likely grossly underestimated. For instance, 17% of Canadians with hypertension are thought to be unaware of their condition (Wilkins 2010). However, bias from undiagnosed diabetes and hypertension would be expected to, if anything, decrease the effect sizes found. The rheumatoid arthritis variable may be inaccurate as CaMos relied on self-report of the diagnosis and many individuals with osteoarthritis may have incorrectly identified themselves with this diagnosis. 5.6% of the CaMos population reported having rheumatoid arthritis, whereas the prevalence in the general population is much lower, around 0.7% in the U.S. (Myasoedova 2010). Data on falls in CaMos is quite limited and

therefore our analyses of falls should be considered only as hypothesis generating. All fractures included in the analyses were clinical fractures; morphometric vertebral fractures were not included. All of the prospective cox proportional hazard analyses failed to uncover statistically significant results. This is likely due to low numbers of incident fractures in the relatively small group of subjects with diabetes. The CaMos population is mostly of Caucasian ethnicity and therefore results cannot be extrapolated to other race groups.

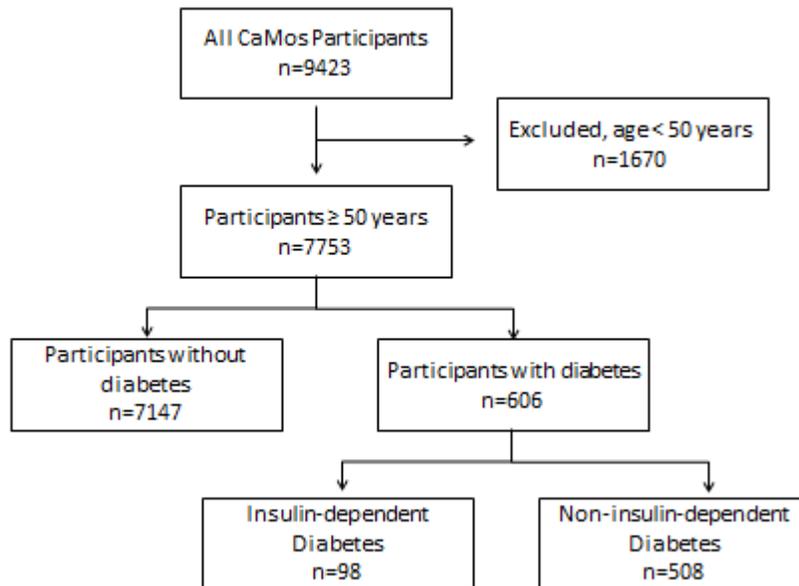
This study raises several important questions and directions for future research. Studies should be performed in other, non-CaMos, populations to confirm that history of cerebrovascular disease and hypertension differentiate patients with diabetes who are at increased fracture risk. Other, diabetes-specific risk factors also need study. Knowledge translation efforts need to be undertaken to educate clinicians involved in the treatment of patients with diabetes about the increased fracture risk and current treatment care gap in diabetics. Lastly, now that diabetics have been identified as a being at increased risk of fracture and we see that they are not getting bone-specific treatment, studies need to be performed to test fracture prevention strategies and therapies specifically in the diabetic population. As mentioned multiple times in this thesis, the pathophysiology of diabetic bone fragility is different from post-menopausal osteoporosis, therefore we cannot assume that current therapies will also necessarily be effective in the diabetic population. There will be an estimated 438 million diabetics globally by 2030 (Houssain 2007) and these therapeutic studies have not yet been performed.

CHAPTER 6 –CONCLUSIONS

In this thesis we found that Canadians with diabetes, both IDDM and NIDDM, are more likely than non-diabetics to have had a non-traumatic fracture. Despite this increased risk, diabetics are less likely to receive fracture prevention therapy with a bisphosphonate. Clinicians that treat individuals with diabetes must therefore be taught to incorporate fracture prevention into the current list of interventions they offer to diabetic patients. Among diabetic patients, those with rheumatoid arthritis, a family history of osteoporosis, decreased BMD, cerebrovascular disease, or hypertension are more likely to have a non-traumatic fracture and therefore these risk factors should be used to flag patients who deserve particular attention.

FIGURES

Figure 1. Flow diagram of selection of CaMos participants used in thesis



TABLES

Table 1. Analysis plan

Outcome	Analysis	Predictor variable ^a	Cohort (reference population)	Time Frame
History of Previous Fracture	1. Logistic Regression	-DM [0=no, 1=type 1, 2=type 2]	All individuals in CaMos >50 yrs old	1) At year 0
Time to incident fracture	2. Cox regression	<i>*Will do both analyses twice, 2nd time DM [0=no, 1=yes, type 1&2]</i>		2) Over years 1-10
History of Previous Fracture among those with diabetes	1. Logistic Regression	- DM [1=type 1, 2=type 2]	Subgroup (just diabetics)	1)At year 0
Time to incident fracture among those with diabetes	2. Cox regression	-Macrovascular disease -Microvascular disease		2) Over years 1-10
Falls	Logistic regression	-DM [0=no, 1=type 1, 2=type 2]	All	Over years 1-10
Bisphosphonte use (defined as use at any point over the 10 years, ie. “ever or never”)	Logistic regression	-DM [0=no, 1=type 1, 2=type 2]	All	Over years 1-10

^aAll analyses also included variables: age, gender, femoral neck T-score, family history of osteoporosis, rheumatoid arthritis, history of non-traumatic fracture.

Table 2. Baseline characteristics of all CaMos participants over 50 years of age and of participants with diabetes

	All CaMos Participants >50 yrs (n=7753)	Insulin-dependent diabetes (n=98)	Non-insulin-dependent diabetes (n=508)
Age (years); mean (SD)	66.7 (9.4)	68.0 (9.0)	69.4 (8.8)
Gender (female)	71.8%	64.3%	65.7%
Femoral Neck BMD T- Score; mean (SD)	-1.24 (0.99)	-0.97 (1.17)	-0.97 (1.04)
Caucasian	95.5%	93.9%	94.3%
Fracture at baseline (n; %)	2133 (27.5)	38 (38.8)	146 (28.7)
BMI; mean (SD)	27.1 (4.78)	29.73 (5.45)	29.06 (5.24)
Years since diagnosis of diabetes; mean;(SD)	N/A	15.4 (11.28)	9.64 (9.60)
Fall/Falls in past month; n(%)	503 (6.5)	11 (11.2)	47 (9.3)
Cigarette use^a; n(%)	4163 (53.7)	54 (55.1)	280 (55.1)
Corticosteroid use^b; n(%)	415 (4.4)	12 (12.24)	33 (6.50)
Alcohol use (per wk); mean (SD)	2.88 (5.85)	1.97 (5.45)	2.27 (6.79)

^aever use daily for > 6 months

^boral or IV, ever use daily for > 1 month

SD: standard deviation, BMD: bone mineral density, BMI: body mass index

Table 3. Outcome variables for all CaMos participants over 50 years of age and of participants with diabetes

Outcome; n(%)	All CaMos Participants >50 yrs (n=7753)	Insulin-dependent diabetes (n=98)	Non-insulin-dependent diabetes (n=508)
Prevalent fracture at study baseline	2133 (27.5)	38 (38.8)	146 (28.7)
Incident fracture over the 10 year study	1189 (15.3)	24 (24.5)	71 (14.0)
Ever bisphosphonate use^a	2188 (28.2)	16 (16.3)	85 (16.7)
Falls^b	2778 (35.8)	38 (38.8)	190 (37.4)

^areported being on a bisphosphonate at any point over the 10 year CaMos study

^breported falls in CaMos questionnaire

Table 4. Variables associated with a history of non-traumatic fracture in all participants in CaMos >50 years of age.

	Without Multiple Imputation; n=4771			With Multiple Imputation; n=7741		
Variable	Odds Ratio	95% Confidence Interval	p-value	Odds Ratio	95% Confidence Interval	p-value
IDDM	2.43	1.39-4.23	0.002	1.82	1.20-2.77	0.005
NIDDM	1.44	1.11-1.87	0.006	1.11	0.90-1.36	0.320
Age: 60-69 yrs	1.13	0.96-1.33	0.144	1.09	0.95-1.25	0.220
70-79 yrs	1.41	1.19-1.68	<0.001	1.26	1.09-1.45	0.002
80-89 yrs	1.42	1.07-1.89	0.150	1.12	0.91-1.37	0.303
≥90 yrs	0.69	0.15-3.23	0.639	2.00	1.13-3.54	0.018
Gender (female)	1.03	0.89-1.19	0.722	1.13	1.00-1.27	0.045
FN T-Score (increasing score)	0.76	0.70-0.81	<0.001	0.79	0.75-0.84	<0.001
Family History of Osteoporosis	1.35	1.15-1.59	<0.001	1.26	1.10-1.45	0.001
Rheumatoid Arthritis	1.44	1.13-1.83	0.004	1.34	1.10-1.63	0.003

IDDM: insulin dependent diabetes mellitus, NIDDM: non-insulin dependent diabetes mellitus, FN: femoral neck

Table 5. Variables associated with a history of non-traumatic fracture in diabetic participants in CaMos >50 years of age

	Without Multiple Imputation; n=335			With Multiple Imputation; n=597		
Variable	Odds Ratio	95% Confidence Interval	p-value	Odds Ratio	95% Confidence Interval	p-value
Gender (female)	1.03	0.89-1.20	0.686	1.13	1.00-1.27	0.045
Age: 60-69 yrs	1.12	0.95-1.33	0.166	1.07	0.93-1.22	0.370
70-79 yrs	1.35	1.13-1.61	1.001	1.20	1.03-1.39	0.017
80-89 yrs	1.35	1.01-1.91	0.044	1.03	0.83-1.27	0.793
≥ 90 yrs	n/a	n/a	n/a	1.80	1.01-3.20	0.046
FN T-Score (increasing score)	0.76	0.71-0.82	<0.001	0.79	0.75-0.84	<0.001
Family History of Osteoporosis	1.36	1.16-1.61	<0.001	1.27	1.10-1.46	0.001
Rheumatoid Arthritis	1.40	1.09-1.79	0.008	1.30	1.07-1.59	0.009
Stroke or TIA	1.65	1.22-2.23	0.001	1.51	1.20-1.91	<0.001
Myocardial infarction	1.21	0.94-1.57	0.139	1.10	0.90-1.33	0.347
Hypertension	1.11	0.96-1.28	0.159	1.16	1.04-1.29	0.010
Kidney disease	1.30	0.79-2.13	0.296	1.09	0.73-1.61	0.681

FN: femoral neck, TIA: transient ischemic attack

Table 6. Hazard ratios for time-to-incident-fracture in diabetic participants in CaMos >50 years of age.

Variable	Hazard Ratio	95% Confidence Interval	Significance
Age: 60-69 yrs	1.32	0.64-2.74	0.452
70-79 yrs	2.21	0.98-4.98	0.055
80-89 yrs	2.53	1.04-6.18	0.042
≥ 90 yrs	2.53	0.22-29.17	0.457
Gender (female)	1.21	0.61-2.35	0.568
Femoral neck T-score (increasing score)	1.11	0.88-1.42	0.377
Family history of osteoporosis	0.71	0.34-1.49	0.362
Rheumatoid arthritis	1.22	0.63-2.37	0.553
History of fragility fracture	0.75	0.47-1.19	0.217
Cerebrovascular disease (stroke or TIA)	1.15	0.56-2.36	0.711
Myocardial infarction	1.64	0.84-3.21	0.149
Hypertension	0.94	0.57-1.56	0.818
Kidney disease	2.21	0.83-5.87	0.111

Table 7. Variables associated with increased risk of reporting a fall over the 10 year CaMos study.

Variable	Odds Ratio	95% Confidence Interval	Significance
Gender (Female)	1.36	1.22-1.51	<0.001
Cerebrovascular disease	1.06	0.84-1.33	0.626
Hypertension	1.04	0.94-1.16	0.414
Diabetes	1.13	0.95-1.35	0.163

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