Improvement and remission of prediabetes and type 2 diabetes mellitus following laparoscopic sleeve gastrectomy

by

© Kendra Kristina Lester

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ABSTRACT

Purpose: To determine the proportion of patients experiencing improvement or remission of prediabetes or type 2 diabetes mellitus (T2DM) 12 months following laparoscopic sleeve gastrectomy (LSG).

Methods: From May 2011 to September 2013, 171 patients underwent LSG and consented to participate in the study. Based on laboratory values, medical history, and antidiabetic medication use, 24 (14.0%) patients had prediabetes and 67 (39.2%) had T2DM. Re-evaluation of laboratory values and medication use was conducted at 3, 6, and 12 months post-surgery to assess for changes in glycemic control and diabetes status.

Results: Of 11 prediabetic patients that returned 12 months post-surgery, 9 (81.8%) achieved remission of prediabetes. 6 of 24 (25%) T2DM patients that returned for 12 month follow-up achieved remission and 5 (20.8%) experienced improvement of T2DM.

Conclusions: Obese patients may experience improvement or remission of prediabetes or T2DM within 12 months following LSG. The mechanisms by which improvement or remission occur are not fully understood. More research is needed to determine the long-term implications of LSG on T2DM complications, prevalence, mortality, etc. before it can be considered as a treatment for prediabetes or T2DM.

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%AWL	percent absolute weight loss
%EWL	percent excess weight loss
2hPG	two hour plasma glucose
A1c	glycated hemoglobin
ADA	American Diabetes Association
BMI	body mass index
BPD	biliopancreatic diversion
CDA	Canadian Diabetes Association
CK	Dr. Christopher S. Kovacs
DPP-4	dipeptidyl-peptidase-4
DS	duodenal switch
FPG	fasting plasma glucose
GIP	gastric inhibitory polypeptide
GLP-1	glucagon-like peptide-1
HDL	high-density lipoprotein
IDF	International Diabetes Federation
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
kg	kilograms
KL	Kendra Lester
LAGB	laparoscopic adjustable gastric banding
LDL	low-density lipoprotein
LSG	laparoscopic sleeve gastrectomy

LRYGB	laparoscopic Roux-en-Y gastric bypass
MONICA	Monitoring of Trends and Cardiovascular Disease
NL	Newfoundland and Labrador
NL BaSco	Newfoundland and Labrador Bariatric Surgery Cohort
OGTT	oral glucose tolerance test
p	probability value
PYY	peptide-YY
RCT	randomized controlled trial
RYGB	Roux-en-Y gastric bypass
SD	standard deviation
SPSS	Statistical Package for the Social Sciences
T2DM	type 2 diabetes mellitus
TRPBC	Translational Research Program in Bariatric Care
WHO	World Health Organization

Chapter 1: Introduction

1.1 Background and Rationale

Obesity is defined as a condition of abnormal or excessive fat accumulation in adipose tissue to such an extent that health may be adversely affected (WHO Consultation on Obesity, 2000). Obesity was recently recognized as a disease by the American Medical Association (American Medical Association, 2013) and is a risk factor for the development of comorbid conditions such as hypertension, type 2 diabetes mellitus (T2DM), cardiovascular disease, osteoarthritis, sleep apnea, certain cancers, and premature mortality (Picot et al., 2009). The amount of excess fat, its distribution throughout the body, and the associated comorbidities can vary between individuals living with obesity (WHO Consultation on Obesity, 2000). Overweight and obesity are most commonly classified by an individual's body mass index (BMI) and is calculated using an individual's height and weight with units kg/m^2 (WHO Consultation on Obesity, 2000). Overweight is defined as $25\ kg/m^2 \leq BMI < 30\ kg/m^2$, whereas obesity is defined as $BMI \geq 30\ kg/m^2$ and is broken down by Health Canada into three separate classes, Class I ($30\ kg/m^2 \leq BMI < 35\ kg/m^2$), II ($35\ kg/m^2 \leq BMI < 40\ kg/m^2$), and III ($BMI \geq 40\ kg/m^2$), with an increased risk of developing health problems as BMI increases (Health Canada, 2003).

BMI is an indirect surrogate measure of body fat commonly used in clinical settings and epidemiological studies (WHO Consultation on Obesity, 2000). It is useful as a crude measure of population-level weight status and a reasonably reliable screening tool, as it correlates highly with direct measure of excess fat and health risk (Belle et al.,

2007). However, the accuracy of BMI may vary on an individual level as it does not distinguish between fluid retention versus adiposity, cases of extreme height or muscle mass, ethnic differences on body composition, or the location of fat (WHO, 1995; Wellens et al., 1996). Alternatively, waist circumference is a convenient and simple measurement that correlates closely with BMI but is unrelated to height and is an approximate measurement of intra-abdominal fat mass and total body fat (WHO Consultation on Obesity, 2000).

Excess abdominal fat is a risk factor for high blood pressure, high cholesterol, T2DM, heart disease, and stroke (Heart & Stroke Foundation, 2010). Males and females with waist circumferences greater than 102 cm and 88 cm, respectively are at an increased risk for developing health problems (Heart & Stroke Foundation, 2010). Decreases in waist circumference reflect decreases in risk factors for cardiovascular disease and other chronic diseases as mentioned above, though the risks vary in different populations (WHO Consultation on Obesity, 2000). Obesity, particularly abdominal obesity, is a well-known risk factor for the development of prediabetes and T2DM. Abdominal fat promotes the secretion of inflammatory chemicals from adipose cells which decreases insulin sensitivity by disrupting the function of insulin responsive cells and their ability to respond to insulin (Diabetes UK, 2014). Adipose tissue also secretes a large number of proteins such as adipsin/ASP and resistin, which decrease insulin sensitivity (Lazar, 2005). This condition is known as insulin resistance and is a trigger for the development of T2DM (Diabetes UK, 2014).

Diabetes is a chronic condition considered by many to be the model chronic disease; it is progressive, managed rather than cured, and creates a burden on both patients and the health care system (Purnell & Flum, 2009). Diabetes can lead to long-term complications affecting the eyes, kidneys, and nerves (Goldenberg & Punthakee, 2013; Maggio & Pi-Sunyer, 2003) and adults with diabetes are two to four times more likely to have a stroke or develop heart disease (American Heart Association, 2012). The Canadian Diabetes Association (CDA) defines the clinical diagnosis of diabetes as based on blood glucose levels, specifically a 2-hour plasma glucose in a 75g oral glucose tolerance test (2hPG in a 75g OGTT) ≥ 11.1 mmol/L, or levels of fasting plasma glucose (FPG) ≥ 7.0 mmol/L, or glycated haemoglobin (A1c) ≥ 6.5% (Goldenberg & Punthakee, 2013). There are three main types of diabetes, type 1 diabetes, T2DM, and gestational diabetes with T2DM being the most common worldwide [International Diabetes Federation (IDF), 2013].

T2DM is a multifactorial disease characterized by high blood glucose levels resulting from the body's inability to produce, secrete, or use insulin properly (Abbatini et al., 2012; Canadian Diabetes Association, 2014; Goldenberg & Punthakee, 2013). The development of T2DM is characterized by resistance to insulin action but it is also associated with progressive β-cell failure in the pancreas and impaired actions of the incretin hormones (Abbatini et al., 2012; Opinto et al., 2013; Zimmet & Alberti, 2012). Incretins, namely glucagon-like-peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are gastrointestinal hormones that stimulate a decrease in blood glucose levels by causing the β-cells in the pancreas to secrete insulin (Opinto et al.,

2013). Incretins also regulate postprandial glucose disposal through the inhibition of glucagon secretion and delayed gastric emptying (Opinto et al., 2013). Furthermore, GLP-1 has an inhibitory effect on appetite and food intake and its impaired effects in individuals with T2DM may explain why the majority of patients with diabetes are overweight or obese (Gutzwiller et al., 1999). While there does not appear to be a major secretory defect in GIP secretion in diabetic patients, the actions of GIP are severely impaired (Opinto et al., 2013). On the other hand, there is a decreased secretion of GLP-1 in diabetic patients, particularly following ingestion of a mixed meal as well as a reduced potency in the insulinotropic effects of GLP-1 in patients with T2DM (Opinto et al., 2013).

In both 1997 and again in 2003, the American Diabetes Association's Expert Committee on Diagnosis and Classification of Diabetes Mellitus identified a group of individuals whose glucose levels were elevated from normal but not enough to meet the criteria for the diagnosis of T2DM [American Diabetes Association (ADA), 2013]. These individuals were referred to as having impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). IFG is defined as FPG levels ranging from 6.1 mmol/L to 6.9 mmol/L while IGT is defined as 2hPG in a 75g OGTT levels between 7.8 mmol/L and 11.0 mmol/L (Goldenberg & Punthakee, 2013). The condition of IGT is more strongly associated with cardiovascular disease outcomes than is IFG (Goldenberg & Punthakee, 2013). These conditions of IFG and IGT are now commonly known as prediabetes (ADA, 2013; Goldenberg & Punthakee, 2013). Individuals living with prediabetes are considered to be at a relatively high risk for developing T2DM and cardiovascular disease in the

future; however, not all individuals with prediabetes will progress to T2DM (ADA, 2013; Goldenberg & Punthakee, 2013).

Preventing, or delaying, the onset of T2DM in high-risk individuals and those living with prediabetes is possible. The Diabetes Prevention Program research group studied the effects of lifestyle modifications and metformin use in reducing the incidence of T2DM in patients with elevated glycemic levels (Knowler et al., 2002). The results of this study found that both lifestyle modification and the use of metformin reduced the incidence of T2DM in prediabetic patients with lifestyle modification being more effective than the use of metformin (Knowler et al., 2002). It follows that both the CDA and the American Diabetes Association (ADA) recommend lifestyle modifications including a 5-7% loss of body weight as well as regular physical activity (150min/week) to prevent the progression of prediabetes to T2DM, with the use of metformin being recommended for very high-risk individuals (ADA, 2013; Ransom et al., 2013).

A patient-centred approach to the management of T2DM is stressed by organizations worldwide. While some individuals are able to manage their diabetes through lifestyle modifications, particularly weight loss and physical activity, the majority of individuals require pharmacological intervention (Zimmet & Alberti, 2012). The initial recommended treatment, if not contraindicated, is metformin; but due to the progressive nature of T2DM most individuals will require the use of multiple medications and then eventually insulin therapy (ADA, 2013; Harper et al., 2013).

T2DM is closely associated with obesity. The prevalence of T2DM and obesity are increasing in parallel worldwide and an estimated 90% of individuals living with T2DM are overweight or obese (Abbatini et al., 2012; Maggio & Pi-Sunyer, 2003; Zimmet & Alberti, 2012). From a global perspective, it is estimated that 382 million people or 8.3% of the adult population worldwide are living with diabetes (IDF, 2013) while 35% of the world's adults are overweight and 12% are obese (WHO Global Health Observatory, 2014). From a Canadian perspective, Newfoundland and Labrador (NL) has the highest prevalence of both diabetes [Canadian Diabetes Association (CDA), 2010a] and obesity (Twells et al., 2014) in the country, 9.3% and 27.7% respectively. Recently, bariatric surgery was recommended as an innovative treatment option for the management of T2DM in obese patients (Buchwald & Oien, 2013; Mechanick et al., 2013; Wharton et al., 2013).

Bariatric surgery is currently the most effective and sustainable treatment for obesity and is one of the most commonly performed gastrointestinal procedures worldwide (Buchwald & Oien, 2013; Mechanick et al., 2013). There are many different types of bariatric surgical procedures and they can be classified as being restrictive, malabsorptive, or a combination of both. With respect to surgical technique, there has been a shift towards performing surgeries laparoscopically as opposed to open surgery as it decreases time spent in the hospital as well as recovery time for patients. Some of the more popular procedures are gastric bypass, biliopancreatic diversion, adjustable gastric banding, and laparoscopic sleeve gastrectomy (LSG).

LSG is a non-reversible, restrictive surgical procedure in which approximately 75%-80% of the stomach is removed, leaving behind a "sleeve" with a reduced gastric volume of 60-100 mL (Karmali et al., 2010; Porier et al., 2011). Once considered to be an investigational procedure, LSG has been growing in popularity amongst surgeons and patients and in 2013 was recommended as a primary bariatric and metabolic procedure to be performed in patients requiring weight loss and/or metabolic control (Mechanick et al., 2013). LSG has been shown to produce good short-term weight loss in patients. One randomized controlled trial found that patients lost 27.9% of their total body weight one year post-surgery (Victorzon, 2012). Clinically expected percent excess weight loss (%EWL) within 6 to 36 months following LSG is 45-60%, and occurs rapidly after surgery (Victorzon, 2012). A Canadian study, with an average follow-up time of 10 months (range: 2–23 months) found that patients had an average weight loss of 27.4 kg and experienced an average change in BMI of 10.4 kg/m^2 (Behrens et al., 2011). In Canada, eligible patients for bariatric surgery are those with class II obesity ($35\ kg/m^2 \leq BMI \leq 40\ kg/m^2$) and one or more obesity-related comorbidity or those with class III obesity ($BMI \geq 40\ kg/m^2$; Lau et al., 2007).

While the mechanism by which improvement or remission of T2DM occurs following bariatric surgery is complex and not fully understood, it appears to be due, in part, to weight loss. However, the degree of improvement does not always correlate with the amount of weight lost increasing the likelihood of the involvement of gut hormones and diet in comorbid resolution following surgery (Poirier & Auclair, 2014).

In May 2011, a new bariatric surgery program began offering residents of NL access to LSG in their own province. At the same time the Translational Research Program in Bariatric Care commenced with the aim of bringing together a team of researchers, health care professionals, and policy and decision makers to design and carry out meaningful research projects to address gaps in the literature surrounding LSG, a relatively new stand-alone bariatric procedure. One of the emerging research projects was an inception cohort study [i.e., Newfoundland and Labrador Bariatric Surgery Cohort Study (NL BaSco study)]. The overall purpose of the study was to examine short-, mid-, and long-term clinical (weight loss and resolution of comorbidities), economic (health services use and costs), and quality of life outcomes in patients undergoing LSG in NL.

In 2011, when this study began, LSG was considered to be an investigational procedure with limited research on the outcomes of LSG with respect to weight loss, complications, and the effect on comorbid conditions such as T2DM (Mechanick et al., 2008). Although there are an increasing number of studies published on LSG outcomes there is a lack of Canadian data on this relatively new procedure. With the start of a bariatric program in NL there is a unique opportunity to study the short-, mid-, and long-term outcomes of LSG. With the recent shift in thinking of bariatric surgery as not only a treatment for obesity but also as a potential treatment for T2DM, this research will add to the current literature on the effectiveness of LSG in treating T2DM from a Canadian health care perspective.

1.2 Purpose

The primary purpose of this arm of the larger cohort study was to investigate the effectiveness of LSG in improving or inducing remission of prediabetes or T2DM in bariatric surgery patients living in NL by determining the proportion of patients experiencing improvement or remission of prediabetes or T2DM 12 months post-surgery, taking into consideration the concomitant use of diabetes medications. A second purpose was to investigate changes in: (1) laboratory values including: FPG, A1c, fasting lipid panel, triglycerides; (2) blood pressure, weight; and (3) dosage and number of antidiabetic medications prescribed.

The study was designed to answer the following primary research questions:

1. What proportion of patients experience improvement or remission of prediabetes 12 months following LSG? What changes, if any, occur in levels of FPG and A1c in prediabetic patients 12 months following surgery?
2. What proportion of patients experience improvement or remission of T2DM 12 months following LSG? What changes, if any, occur in levels of FPG and A1c in patients with T2DM 12 months following surgery?

The secondary research questions addressed by this study were:

1. What baseline factors, if any, can be used to predict the likelihood of a patient achieving remission of prediabetes or T2DM 12 months post-surgery?
2. Is the amount of weight lost 12 months post-surgery associated with changes in blood pressure or levels of FPG, A1c, triglycerides, high-density lipoprotein

(HDL), low-density lipoprotein (LDL), or total cholesterol post-surgery? Is the amount of weight lost associated with remission of prediabetes or T2DM 12 months post-surgery?

3. What changes, if any, occur in weight, blood pressure, triglycerides, and fasting lipid panel levels, and dose and number of antidiabetic medications prescribed 12 months post-surgery?

Chapter 2: Literature Review

The purpose of this literature review is to review and summarize the gaps in the clinical literature on the remission or improvement of prediabetes and T2DM following LSG. First will be an overview of obesity, prediabetes, T2DM, and bariatric surgery from a global, national, and provincial perspective. Second will be a review of the literature comparing the effectiveness of LSG to other types of bariatric surgery in resolving T2DM followed by a review of the existing literature on the efficacy of LSG in resolving T2DM.

2.1 Epidemiology of Obesity

2.1.1 Global trends. The prevalence of overweight and obesity is increasing in both developed and developing countries (Stevens et al., 2012; WHO Consultation on Obesity, 2000). In 2008, 1 in 3 adults worldwide was overweight and 1 in 9 was obese (Stevens et al., 2012). A paper by Stevens et al. (2012) estimated trends in overweight and obesity in 199 countries and found that the age-standardized prevalence of obesity nearly doubled from 6.4% to 12.0% between 1980 and 2008, with half of this increase occurring in the last 8 years, from 2000 to 2008. During this same period, the global prevalence of overweight increased from 24.4% to 34.4%. Not only are obesity rates continuously rising globally, but the rate of growth appears to have accelerated in the last decade (Stevens et al., 2012).

Obesity rates vary by country and region. In 2008, the highest obesity prevalence was found in the regions of North Africa and Middle East, Central and Southern Latin America, Southern Sub-Saharan Africa, and North America with prevalences ranging from 27.4% to 31.1% (Stevens et al., 2012). Based on the most recent data available from

the World Health Organization (WHO), the countries with the highest percentage of obese adults (BMI ≥ 30 kg/m^2) were Nauru (78.5%), American Samoa (74.6%), and Tokelau (63.4%) (WHO, 2012a). The lowest percentage of obese adults was found in Vietnam (0.5%), India (0.7%), and Lao People's Democratic Republic (1.2%) (WHO, 2012a). The WHO Monitoring of Trends and Cardiovascular Disease (MONICA) study reported that, in general, women have higher rates of obesity than men whereas men may have higher rates of overweight than women (WHO Consultation on Obesity, 2012).

2.1.2 Obesity in Canada. Obesity rates are rising in Canada. The prevalence of adult obesity (BMI ≥ 30 kg/m^2) increased from 6.1% in 1985 to 18.3% in 2011 (Twells et al., 2014). During this time the prevalence of all obese classes increased and disproportionate increases were seen in the higher classes of obesity (Twells et al., 2014). Rates of overweight in Canada are also rising with an increase from 27.8% in 1985 to 33.6% in 2011 (Twells et al., 2014). Based on the most recent self-reported data available from Statistics Canada (2013), 62.0% of males and 45.1% of females in Canada are overweight or obese.

Just as obesity rates vary globally between countries and within regions, obesity rates in Canada vary by province and territory. Data of self-reported obesity rates in 2011 varied from a low of 14.5% in British Columbia to a high of 27.7% in Newfoundland and Labrador (Twells et al., 2014). In fact, the prevalence of obesity in all provinces and territories increased in the period between 2000/1 and 2011 (Twells et al., 2014). In general, lower prevalence rates of obesity were observed in western Canada compared to eastern Canada and from a regional perspective, the prevalence of obesity tends to be

lower in urban areas compared to rural areas (Twells et al., 2014). Similar trends have been reported in the prevalence of overweight in Canada, the lowest prevalence being 31.3% in British Columbia and the highest being 41.8% in Newfoundland and Labrador. In contrast, between 2000/1 and 2011 the provinces of Prince Edward Island, New Brunswick, and Alberta have experienced slight decreases in the prevalence of overweight individuals (Twells et al., 2014).

2.1.3 Obesity in Newfoundland and Labrador. NL has the highest prevalence of overweight and obesity in the country. In 2013, self-reported data from Statistics Canada indicated that 69.2% of the population was overweight or obese (Statistics Canada, 2013). A recent study by Twells et al. (2014) using data from the Statistics Canada Canadian Community Health Surveys reported that in 2011 the prevalence of obesity in NL was 27.7%, indicating that approximately 1 in 3 adults was obese (BMI $\geq$ 30 kg/m^2). In ten years, between 2000/1 and 2011, the prevalence of overweight increased from 38.2% to 41.8% and the prevalence of obesity increased from 21.7% to 27.7% (Twells et al., 2014). This increase in the prevalence of obesity in the province was accompanied by an increase in all three classes of obesity between 2000/1 and 2011 from 16.1% to 20.5% for obese class I, 4.1% to 4.6% for obese class II, and 1.5% to 2.6% for obese class III (Twells et al., 2014). The most alarming prediction in the study by Twells and colleagues is that by 2019 an estimated 71% of the adult population in NL will be overweight or obese and increases in the prevalence of all obese classes are predicted.

2.2 Obesity: Etiology & Health Risk

Obesity is a disease in which excess body fat has accumulated to the extent that health may be adversely affected and can be viewed, conceptually, as the physical manifestation of chronic excess energy (Sharma & Padwal, 2010; WHO Consultation on Obesity, 2000). The etiology of obesity is complex and multifactorial and results from a range of etiologies that promote long-term positive energy balance (Lau et al., 2007; Sharma & Padwal, 2010). The relationship between body weight, energy intake and expenditure can be illustrated by a simple equation:

$$\text{Energy}_{\text{intake}} - \text{Energy}_{\text{expenditure}} = \Delta \text{ Body Weight}$$

Multiple factors such as diet, metabolism, and physical activity contribute to an individual's energy intake and expenditure, and a change in any of these factors, if not corrected, will result in a net imbalance of energy, which, if positive, will lead to weight gain (Sharma & Padwal, 2010). An individual's metabolic rate, or resting energy expenditure, is influenced by their age, gender, sarcopenia, neuroendocrine function, metabolically active fat, previous weight loss, and medication use (Sharma & Padwal, 2010). Increased energy intake by over-eating may be influenced by socio-cultural factors, mindless eating, a lack of knowledge about healthy eating, food availability, emotional over-eating, certain psychiatric disorders, sleep deprivation, and medication use (Sharma & Padwal, 2010). Physical inactivity is also a risk factor for weight gain and is influenced by socio-cultural factors, musculoskeletal pain, injury, psychiatric disorders, and medication use (Sharma & Padwal, 2010). Lifestyle interventions, such as the modification of diet and physical activity, remain the main course of treatment for

obesity; but, adherence is poor and results in modest long-term success (Lau et al., 2007). Pharmacotherapy and bariatric surgery in adjunct with lifestyle interventions have been proven to improve health outcomes of overweight and obese individuals (Lau et al., 2007).

Obesity is a major risk factor for the development of many health disorders such as hypertension, T2DM, cardiovascular disease, osteoarthritis, sleep apnea, certain cancers, and premature mortality (Picot et al., 2009). Obesity has also been shown to negatively impact mental, emotional, and psychosocial health (WHO Consultation on Obesity, 2000). Non-fatal but debilitating health problems associated with obesity include: respiratory difficulties, chronic musculoskeletal problems, infertility, and skin problems (WHO Consultation on Obesity, 2000).

The severity of obesity health related risk varies with body weight. Underweight, overweight, and obesity in adults is classified by BMI which is defined as an individual's weight in kilograms divided by the square of their height in metres (kg/m^2) (WHO Consultation on Obesity, 2000). The severity of health risk increases with BMI and is illustrated in Table 2.1. A prospective study by Calle et al. (1999) showed that the association between BMI and health risk follows a U-shaped curve with those who were severely underweight or obese being at an increased relative risk of death from all causes. The relative risk of death for obese persons was more than twice of that for persons with BMIs in the normal weight range. This is further supported by results from a national longitudinal study of Canadian adults which found a significant increased risk of mortality in individuals who were underweight (relative risk (RR)=1.73, 95% confidence

interval (CI) 1.25-2.39, $p<0.001$) or in obese Class II or higher (RR=1.36, 95% CI, 1.00-1.85, $p<0.05$) (Orpana et al., 2009). It is important to note that BMI is not the only factor influencing the adverse health consequences of obesity; other factors include the location of body fat, the magnitude of weight gain during adulthood, and a sedentary lifestyle (WHO Consultation on Obesity, 2000).

Table 2.1

BMI Classification for Adults and Associated Risk of Comorbidities

BMI (kg/m^2)	**Health Canada Classification***	**Risk of Comorbidities****
< 18.5	Underweight	Low (increased risk of other clinical problems)
18.5 – 24.9	Normal Weight	Average
25.0 – 29.9	Overweight	Increased
30.0-34.9	Obese Class I	Moderate
35.0 – 39.9	Obese Class II	Severe
≥ 40.0	Obese Class III	Very Severe

Note: *Health Canada, 2003, **WHO Consultation on Obesity, 2000

2.3 Epidemiology of Prediabetes & Type 2 Diabetes Mellitus

2.3.1 Global Trends in T2DM. Diabetes imposes high human, social, and economic costs on countries at all income levels and is considered to be one of the fastest growing epidemics in history (IDF, 2013; Zimmet & Alberti, 2012). The prevalence of diabetes is increasing globally mainly as a result of the rising rates of obesity but also due to the declining mortality of people living with diabetes (Anvari, 2014). Worldwide it is estimated that there are 382 million adults or 8.3% of the adult population living with diabetes and this number is expected to increase 55% by 2035 (IDF, 2013). Furthermore, an estimated 316 million adults (6.9%) have prediabetes, a number that is expected to climb as high as 471 million (8.0%) by the year 2035 (IDF, 2013). The economic burden of diabetes is enormous with 548 billion USD or 11% of the total health spending worldwide spent on diabetes care in 2013 (IDF, 2013). The International Diabetes Federation (IDF) (2013) estimates that 80% of the world's affected population live in low- and middle-income countries where diabetes rates are growing at a fast pace, providing a worrying indication of the future impact of this disease as a major threat to global development.

Different regions of the world are affected to different degrees by diabetes. The smallest diabetes population is seen in Africa and the largest in the Western Pacific. South and Central America are expected to see the population of people living with diabetes increase by 60% by 2035 with the largest increase expected to be seen in Africa (109%) followed closely by the region of Middle East and North Africa (96%). The smallest increase is projected for Europe at a percent change of 22% by 2035. As a result

of rapid development there has been a fast-growing epidemic of diabetes in South-East Asia which now accounts for close to 20% of all cases of diabetes worldwide. Of the seven IDF regions, North America and the Caribbean ranks fifth for the number of people living with diabetes and this number is expected to increase by 37% by 2035 (IDF, 2013).

2.3.2 T2DM in Canada. Diabetes is one of the most common chronic diseases in Canada. In 2008/9, 8.7% of Canadians over the age of 20 were living with diabetes, representing 1 in 11 Canadians [Public Health Agency of Canada (PHAC), 2011], and it is estimated that 90% of these cases are T2DM (Anvari, 2014). In a ten year period from 1998/9 to 2008/9, the prevalence of diabetes among all Canadians increased by 70%, from 3.3% to 5.6%, with the prevalence over time being consistently higher in males than in females (PHAC, 2011). However, the prevalence of diabetes across Canada varies by province and territory. After accounting for differences in age, the lowest prevalence was seen in Nunavut and Alberta at 4.4% and 4.9%, respectively while the highest were in Nova Scotia and Newfoundland and Labrador at 6.1% and 6.5%, respectively (PHAC, 2011). These prevalence rates represent known cases of T2DM and likely underestimate the true prevalence as T2DM is typically present for 5 to 10 years before diagnosis.

One of the contributing factors to the increase in the number of Canadians living with diabetes is the aging population, largely a result of the baby boom cohort (PHAC, 2011). The increased lifespan of people living with diabetes has also contributed to the growing prevalence rates of diabetes in the country (PHAC, 2011). However, while the proportion of people living with diabetes generally increases with age, more than 50% of the affected Canadian population is between the ages of 25 and 64 years (PHAC, 2011).

The proportion of individuals living with diabetes has increased more in younger age groups than in older age groups likely due to increasing rates of overweight and obesity (PHAC, 2011; Lau et al., 2007).

2.3.3 T2DM in Newfoundland and Labrador. NL has the highest prevalence of diabetes in Canada with 9.3% of the population living with diagnosed diabetes (CDA, 2010a). The CDA estimates that the prevalence of diabetes in this province will increase by 56% from 2010 to 2020 (CDA, 2010a). As the prevalence of diabetes increases in NL so will the economic effects on the healthcare system. The economic burden of diabetes in NL is estimated to increase by 27% from $254 million CDN to $322 million CDN by the year 2020 (CDA, 2010b). The population of NL has a higher risk for diabetes than other provinces in Canada for many reasons: NL has the oldest population, the highest rates for overweight and obesity, the highest prediabetes rate, and close to the lowest median family income (CDA, 2010a).

2.4 Prediabetes & Type 2 Diabetes Mellitus: Diagnostic Criteria, Etiology, & Health Risk.

Diabetes is a chronic metabolic disorder that occurs when the pancreas cannot produce enough insulin or the body is unable to use insulin effectively. In T2DM, the body is able to produce insulin but either in insufficient amounts or the body is unable to respond to its effects, known as insulin resistance, leading to a build-up of glucose in the blood known as hyperglycemia (Goldenberg & Punthakee, 2013; IDF, 2013). Prediabetes is a term that refers to an intermediate group of individuals with glucose levels that are elevated from normal but not enough to meet the criteria for T2DM; these individuals are living with impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or both

(ADA, 2013; Goldenberg & Punthakee, 2013). Individuals living with prediabetes are at an increased risk of developing T2DM as well as cardiovascular disease (ADA, 2013). However, it is important to note that not everyone living with prediabetes will go on to develop T2DM, and there is a large body of evidence which supports the effectiveness of lifestyle interventions such as a healthy diet and physical activity to prevent the progression of prediabetes to diabetes (IDF, 2013).

In 2013, the CDA released updated Clinical Practice Guidelines outlining the diagnostic criteria for prediabetes and T2DM which is presented in Table 2.2 and Table 2.3, respectively. The inclusion of glycated haemoglobin (A1c) in the diagnostic criteria for prediabetes and T2DM is new to the 2013 Clinical Practice Guidelines.

People living with T2DM can remain undiagnosed for many years, unaware of the long-term damage being caused by the disease (IDF, 2013). Often diagnosis occurs only when complications of the disease have already developed (IDF, 2013). While the reasons for developing T2DM are still unknown, there are known risk factors which include: obesity, poor diet, physical inactivity, aging, family history of diabetes, and ethnicity (Aboriginal, Hispanic, South Asian, Asian, or African descent) (CDA, 2013; IDF, 2013). Anyone over the age of 40 is at risk for developing T2DM and it is recommended that screening be done every 3 years (CDA, 2013; IDF, 2013).

Table 2.2

*Diagnostic Criteria for Prediabetes**

Test	Result	Prediabetes Category
FPG (mmol/L)	6.1 – 6.9	IFG
2hPG in a 75g OGTT (mmol/L)	7.8 – 11.0	IGT
A1c (%)	6.0 – 6.4	Prediabetes

Note: 2hPG= 2 Hour Plasma Glucose, A1c= Glycated Hemoglobin, FPG= Fasting Plasma Glucose, IFG= Impaired Fasting Glucose, IGT= Impaired Glucose Tolerance, OGTT= Oral Glucose Tolerance Test

*Goldenberg & Punthakee, 2013

Table 2.3

*Diagnostic Criteria for Type 2 Diabetes Mellitus**

FPG ≥ 7.0 mmol/L
or
A1c ≥ 6.5% (in adults)
or
2hPG in a 75g OGTT ≥ 11.1 mmol/L
or
Random PG ≥ 11.1 mmol/L

Note: 2hPG= 2 Hour Plasma Glucose, A1c= Glycated Hemoglobin, FPG= Fasting Plasma Glucose, OGTT= Oral Glucose Tolerance Test, PG= Plasma Glucose
*Goldenberg & Punthakee, 2013

The main pathophysiological factors contributing to the onset of T2DM are insulin resistance and β-cell dysfunction (Taylor, 2013). Whole-body insulin resistance is the earliest predictor of T2DM with the earliest detection of insulin resistance found in skeletal muscle (Taylor, 2013). Insulin resistance may be caused by an insulin signalling defect, a glucose transporter defect, or lipotoxicity (Taylor, 2013). In contrast, β-cell dysfunction resulting in changes in insulin secretion determines the onset of hyperglycemia as well as the progression towards insulin-based therapy (Taylor, 2013). It is suggested that β-cell dysfunction may be caused by amyloid deposition in the islets, oxidative stress, excess fatty acid, or lack of incretin effect (Taylor, 2013). Excess fat inhibits β-cell functioning and there is now clear evidence that weight loss reverses β-cell defects at least early in the course of T2DM (Taylor, 2013).

Furthermore, an accumulation of fat in the liver may also increase an individual's risk of developing T2DM (Taylor, 2013). Storage of fat in the liver occurs only when there is an overall energy imbalance, i.e., when daily caloric intake exceeds energy expenditure (Taylor, 2013). Decreasing the amount of fat stored in the liver has been associated with an improvement in insulin suppression of glucose production resulting in an improvement of FPG (Taylor, 2013). An overall energy imbalance leads to excess fat in the pancreas as well as in the liver, which promotes the development of T2DM (Taylor, 2013); however, it also leads to individuals being overweight or obese which may explain why the majority of patients with T2DM are overweight or obese. Abdominal fat is of particular concern as it promotes the secretion of inflammatory chemicals from adipose cells, which disrupts the ability of insulin responsive cells to respond to insulin thus

promoting insulin resistance and triggering the development of T2DM (Diabetes UK, 2014).

The development of prediabetes and T2DM is also characterized by impaired actions of the incretin hormones, specifically GIP and GLP-1. Recent studies suggest that impaired incretin effects are an early sign of impaired glucose metabolism with further impairment occurring as glucose intolerance develops (Opinto et al, 2013). Incretins are gastrointestinal hormones that stimulate a decrease in blood glucose levels by causing the β-cells in the pancreas to secrete insulin (Opinto et al., 2013). These hormones also regulate postprandial glucose disposal through the inhibition of glucagon secretion and delayed gastric emptying (Opinto et al., 2013). GIP is insulinotropic and its secretion in diabetic patients is near normal, however, its effect on insulin secretion in the presence of T2DM is severely impaired (Holst et al., 2009). Glucagon is a peptide hormone produced by α-cells in the pancreas that promotes the conversion of glycogen to glucose in the liver thus increasing blood glucose levels. Diabetic patients experience hyperglucagonemia as well as an increased glucagon response following a meal (Holst et al., 2009). One important antidiabetic action of GLP-1 is the inhibition of glucagon production, limiting the conversion of glycogen to glucose in the liver (Nauck et al., 2002). While GLP-1 secretion is impaired in diabetic patients, the potency of its effect on insulin secretion and glucagon-suppression is decreased in diabetic patients compared to healthy subjects. These changes in GIP action and GLP-1 secretion and action cause blood glucose levels to be elevated from normal (Holst et al., 2009).

The rate of gastric emptying and the secretion and action of the incretin hormones are major determinants of postprandial glycemia (Marathe et al., 2013). While rates of gastric emptying vary within individuals, patients with diabetes frequently experience abnormally delayed gastric emptying, or gastroparesis (Marathe et al., 2013). Postprandially, the magnitude of the incretin effect is dependent on the rate of gastric emptying, i.e., the incretin effect should be greater in a person whose stomach empties at a rate of 4 kcal/min compared to a rate of 2 kcal/min (Marathe et al., 2013); thus, the incretin effect is impaired in diabetic patients with gastroparesis. In individuals with T2DM the magnitude of the GLP-1 response is crucial as the insulinotropic effects of GIP are reduced (Marathe et al., 2013). Furthermore, GLP-1 has an inhibitory effect on appetite and food intake (Holst et al., 2009); however, with the impaired incretin effects that accompany T2DM the effects of GLP-1 in promoting satiety are lessened and may help explain why many patients with T2DM are overweight or obese (Gutzwiller et al., 1999).

Obese subjects with normal glucose tolerance have been reported to experience a reduced incretin effect potentially increasing their risk for the development of prediabetes and T2DM (Opinto et al., 2013). Following a mixed meal and glucose ingestion, the secretion of GLP-1, but not of GIP, is reduced in obese subjects and there is evidence indicating the existence of an inverse relationship between body weight and levels of GLP-1 (Opinto et al., 2013). In patients living with T2DM the loss of these incretin effects is more extensive in obese than in lean patients (Opinto et al., 2013).

Fasting lipid panel levels may also be indicative of T2DM. The most common lipid pattern in people living with T2DM consists of elevated levels of triglycerides, low levels of high-density lipoprotein cholesterol (HDL), and relatively normal concentrations of low-density lipoprotein cholesterol (LDL) and is often referred to as diabetic dyslipidemia (Ginsberg et al., 2005; Mancini et al., 2013). There is substantial evidence supporting a key role for insulin resistance as a central pathophysiological feature of T2DM in the development of diabetic dyslipidemia (Ginsberg et al., 2005). A common characteristic of insulin resistance dyslipidemia is increased postprandial hyperlipidemia and, while clearance of postprandial triglycerides is usually reduced, an increased production of triglyceride carrying molecules, chylomicron particles, may also play a role (Ginsberg et al., 2005). Thus, as T2DM improves, or remission is achieved, and insulin resistance decreases, there should be an improvement in triglyceride serum levels.

People living with diabetes are at risk of developing a number of serious health problems. Diabetes is considered a leading cause of blindness, end-stage renal failure, and lower limb amputations as well as a major risk factor for cardiovascular disease (Dixon et al., 2005; Doggrell & Chan, 2012; IDF, 2013; Maggio & Pi-Sunyer, 2003). Though there are many treatments available for T2DM, more than 60% of individuals living with T2DM die from heart disease or stroke (Doggrell & Chan, 2012). In 2013, 5.1 million deaths worldwide were attributed to diabetes and this number is expected to increase significantly as a result of the rise in the global prevalence of diabetes (IDF, 2013).

2.5 Obesity & Type 2 Diabetes Mellitus

The relationship between obesity and T2DM is undisputable and is further established by the fact that the prevalence of both are increasing in parallel (Anvari, 2014). The term “diabesity” has been coined to demonstrate the close link between these chronic conditions (Dixon et al., 2005).

Overweight, and especially visceral adiposity, are important risk factors for the development of T2DM and its complications and are considered to be the driving force behind the rising prevalence of T2DM. It is estimated that 80% to 90% of T2DM cases can be attributed to overweight and obesity (Abbatini et al., 2012; Wharton et al., 2013). Historically, T2DM has been considered a disease of the aged with most patients being diagnosed after the age of 40 years; however, in recent years there has been an emergence of T2DM diagnoses among overweight and obese adolescents and youth highlighting the serious health consequences of obesity on all age groups (Maggio & Pi-Sunyer, 2003; PHAC, 2011).

A study from the United States estimates that, at birth, the risk of developing diabetes is 1 in 3; however, this risk can be modified by weight and BMI (Narayan et al., 2007). Narayan and colleagues (2007) further investigated the impact of BMI on the lifetime risk of diabetes and discovered that in males 18 years of age the lifetime risk of developing diabetes for those with BMI < 18.5 kg/m^2 was 7.6% compared to 70.3% for those with BMI > 35 kg/m^2. A similar result was seen in females whose lifetime risk of diabetes ranged from 12.2% to 74.4% for BMIs <18.5 kg/m^2 and > 35 kg/m^2, respectively (Narayan et al., 2007). The results for males and females at 65 years of age were similar

but not as dramatic as those for individuals 18 years of age. In males 65 years of age the remaining lifetime risk of developing diabetes ranged from 2.2% to 34.7% for BMIs <18.5 kg/m^2 and > 35 kg/m^2, respectively (Narayan et al., 2007). In females 65 years of age the lifetime risk of developing diabetes for those with BMI < 18.5 kg/m^2 was 3.7% compared to 36.0% for those with BMI > 35 kg/m^2 (Narayan et al., 2007). The study concluded that compared to individuals with a lower BMI, individuals living with obesity (BMI ≥ 30 kg/m^2) have a higher risk of developing diabetes, having the disease for a longer period of time, and excess life-years lost to diabetes (Narayan et al., 2007).

Results from the Nurses' Health Study which observed more than 84,000 female nurses further support the idea that the risk of developing T2DM increases with BMI. The study's findings suggested the risk of developing T2DM increased 20-fold for those in obese class I (30.0 kg/m^2 ≤ BMI ≤ 34.9 kg/m^2) and 38-fold for those in obese classes II and III (BMI ≥ 35 kg/m^2) (Maggio & Pi-Sunyer, 2003). The Nurses' Health Study also reported that increasing BMI, increasing weight gain, weight gain after the age of 18 years, and duration of obesity are all positively associated with the development of T2DM (Maggio & Pi-Sunyer, 2003). From the perspective of excess body weight, it is estimated that for each kilogram increase in measured weight the risk of diabetes increases by 4.5% (Maggio & Pi-Sunyer, 2003).

Not only is obesity a risk factor for the development of T2DM but it also has an impact on the disease when both coexist. Obesity increases insulin resistance and glucose intolerance and heightens metabolic abnormalities associated with T2DM such as hyperinsulinemia, hyperglycemia, and dyslipidemia thus complicating the management of

T2DM and making it more difficult to treat pharmacologically (Maggio & Pi-Sunyer, 2003). Furthermore, intensive insulin therapy and some antidiabetic medications such as sulfonylureas and thiazolidinediones promote weight gain which further complicates the management of T2DM in obese patients (Maggio & Pi-Sunyer, 2003; Wharton et al., 2013).

2.6 Weight Management in Prediabetes & Type 2 Diabetes Mellitus

Obesity is a major risk factor for the development of prediabetes and T2DM and causes further complications with these chronic conditions; thus, weight management is an extremely important aspect in the treatment of prediabetes and T2DM. A modest weight loss of 5% to 10% can substantially improve glycemic control (Wharton et al., 2013) and can potentially prevent the succession from prediabetes to T2DM by almost 60% (Ransom et al., 2013). Weight loss improves glycemic control by increasing insulin sensitivity and glucose uptake and diminishing hepatic glucose output (Maggio & Pi-Sunyer, 2003; Wharton et al., 2013). Weight loss in patients living with obesity and T2DM also improves existing comorbidities such as dyslipidemia and hypertension (Maggio & Pi-Sunyer, 2003; Wharton et al., 2013). It follows that the CDA Clinical Practice Guidelines (2013) recommend an interdisciplinary weight management program along with adjunctive pharmacotherapy, if necessary, for overweight and obese people with, or at risk for, T2DM to prevent weight gain and to achieve and maintain a lower, healthy body weight (Wharton et al., 2013).

However, people living with T2DM often have difficulty losing weight due in part to insulin resistance and also to the side effects of weight gain associated with some

antidiabetic medications and insulin therapies (Lau et al., 2007). The clinical practice guidelines recommend that adults with T2DM and either class II or class III obesity may be considered for bariatric surgery when lifestyle interventions are inadequate in achieving healthy weight goals (Wharton et al., 2013).

2.7 Bariatric Surgery

Bariatric (weight loss) surgery is the only intervention proven to promote significant, sustainable weight loss and sustained improvement in weight-related comorbidities in individuals living with obesity (Jackson & Hutter, 2012; Mechanick et al., 2013). Currently there are approximately five bariatric procedures available in Canada and an increasing population of eligible candidates. When lifestyle interventions are unsuccessful in achieving healthy weight goals, patients may be recommended for bariatric surgery based on the following eligibility criteria: BMI $\geq$ 35 kg/m^2 with comorbidities or BMI $\geq$ 40 kg/m^2 (Lau et al., 2007).

The primary bariatric procedures recommended to be performed in patients requiring weight loss are laparoscopic adjustable gastric banding (LAGB), LSG, laparoscopic Roux-en-Y gastric bypass (LRYGB), and laparoscopic biliopancreatic diversion (BPD), BPD/duodenal switch (BPD-DS), or related procedures (Mechanick et al., 2013). All bariatric procedures fundamentally involve altering the digestive system in either a restrictive, malabsorptive, or a combination of restrictive/malabsorptive capacity to induce rapid, sustainable weight loss (Belle et al., 2007; Padwal et al., 2011; Picot et al., 2009). Bariatric procedures that are considered to be restrictive such as LSG and LAGB, physically limit the amount of food, and thereby calories, that an individual can

consume by reducing gastric volume. Malabsorptive procedures restrict nutrient absorption in the small intestine and include BPD and BPD-DS. LRYGB is an example of a bariatric procedure that uses both restriction and malabsorption to help patients lose weight.

In 2011, there were 340,768 bariatric procedures performed worldwide with the majority (101,645) being performed in the USA/Canada (Buchwald & Oien, 2013). The most commonly performed procedures worldwide are Roux-en-Y gastric bypass (RYGB) (46.6%), sleeve gastrectomy (27.8%), and adjustable gastric banding (17.8%) (Buchwald & Oien, 2013) with more than 90% of bariatric surgeries performed laparoscopically through small incision ports in the abdomen (Padwal et al., 2011). It is interesting to note the dramatic increase in popularity of LSG as a bariatric procedure. Buchwald and Williams (2004) reported that LSG accounted for 0% of bariatric surgeries performed worldwide in 2003 and just 8 years later an updated report published by Buchwald and Oien (2013) estimated that LSG accounted for 27.8% of bariatric surgical procedures performed worldwide in 2011. Despite these astonishing figures, it is noted that only 1% of the eligible population receives surgical treatment for obesity (Mechanick et al., 2013).

In NL, LSG is the most common surgical treatment option for obesity. First described in 1988, LSG began as the first stage of a 2-stage procedure in superobese high-risk patients to induce weight loss and lower their operative risk before undergoing a more complicated procedure such as BPD-DS or RYGB (Behrens et al., 2011; Victorzon 2012). Since 1993, LSG has been performed as a stand-alone bariatric procedure demonstrating benefits comparable to other procedures (Mechanick et al., 2013;

Victorzon 2012). In the USA, a national risk-adjusted database placed LSG between LRYGB and LAGB in terms of weight loss, resolution of comorbidities, and complications (Mechanick et al., 2013). It follows that LSG is no longer considered to be investigational and is currently recommended as a primary bariatric procedure by the American Society for Metabolic and Bariatric Surgery (Mechanick et al., 2013). The surgical procedure involves resecting the greater curvature and fundus of the stomach, leaving a tube or a "sleeve" with a volume of 60-100 mL (Behrens et al., 2011; Gill et al., 2010; Padwal et al., 2011).

Weight loss following LSG is attributed to a reduced stomach volume leading to decreased food intake but also to decreases in gastrointestinal hormone levels such as serum ghrelin, a major hunger-inducing hormone (Behrens et al., 2011; Padwal et al., 2011). With respect to incretins, LSG has been shown to increase the post-prandial release of distal gut hormones, namely GIP and GLP-1, to a similar extent as seen following RYGB (Romero et al., 2012). The exact mechanism by which LSG creates favorable weight loss and metabolic changes is not yet fully understood.

A recent systematic review performed by Victorzon (2012) noted that the quantity, quality, and consistency of evidence concerning LSG for the treatment of severe obesity is low. Numerous studies following patients for one to three years post-LSG have shown good results for weight loss; however, there is a lack of long-term published data available for a follow-up of ≥ 5 years with at least 100 patients. There is a similar gap in long-term data surrounding LSG and its impact on the resolution of comorbidities, particularly T2DM. Several small retrospective studies reported an effect on rates of

T2DM remission at four months to three years following LSG (Abbatini et al., 2010; Cassella et al., 2011; Chouillard et al., 2011; Kehagias et al., 2011; Lee et al., 2011; Nocca et al., 2011; Rosenthal et al., 2009; Vidal et al., 2007; Woelnerhanssen et al., 2011). If future long-term studies report weight loss, resolution of comorbidities, and quality of life improvements comparable to the more popular LRYGB, LSG may surpass LRYGB as the bariatric procedure of choice due to its increased simplicity and reduced risk of nutrient deficiencies and surgical risks.

2.7.1 Bariatric Surgery in Newfoundland and Labrador. In May of 2011 the Eastern Health Regional Health Authority of NL introduced LSG as a surgical treatment option for severe obesity. A bariatric surgery clinic, including two bariatric surgeons, a nurse practitioner, and a dietician was established to provide 70-100 LSG surgeries annually. In December 2012, a third bariatric surgeon was recruited and the estimated number of surgeries performed per year is 100.

2.7.2 Bariatric Surgery & Improvement or Remission of T2DM. Although the aim and success of weight loss interventions such as bariatric surgery are often based on the amount of weight lost, improvements in quality of life and comorbidities are generally a more meaningful indication of success for individuals. In the long term, weight loss from surgical interventions is associated with decreased risk of developing T2DM, resolution of T2DM, and a reduction in LDL-cholesterol, total cholesterol, and blood pressure as well as reduced mortality in patient deaths resulting from T2DM, heart disease, and cancer (Picot et al., 2009; Poirier et al., 2011). Of particular interest is the effect of bariatric surgery on preventing T2DM and remission of pre-existing T2DM.

Many studies have examined the effect of bariatric surgery on T2DM and while all types of bariatric surgery have been associated with remission of T2DM, malabsorptive procedures appear to be the most effective (Poirier et al., 2011). Both the ADA and CDA recommend bariatric surgery for obese individuals (BMI $\geq$ 35 kg/m^2) living with T2DM as a viable treatment option for their diabetes (ADA, 2013; Wharton et al., 2013). Small trials have shown the glycemic benefits of bariatric surgery in patients living with T2DM and BMIs of 30-35 kg/m^2 who normally would not be eligible for surgery (ADA, 2013). However, neither the ADA nor the CDA recommend surgery in this patient population as current evidence is limited by the number of subjects studied and the lack of long-term data demonstrating net benefit (ADA, 2013; Mechanick et al., 2013; Wharton et al., 2013).

2.7.3 Effects of LSG vs. LAGB & RYGB on Improvement or Remission of T2DM. It is well known that bariatric surgery is the most effective treatment for severe obesity but evidence is emerging to suggest that it may also be effective in inducing remission of T2DM, with the results varying by the type of operation. Often this effect occurs before significant amounts of weight are lost; thus, it is thought to be a result of changes in gut hormones and diet. Numerous studies have examined the effects of LSG, LAGB, and LRYGB independently on the improvement or remission of T2DM but fewer studies have directly compared the effects of LSG versus either LAGB or LRYGB. Two meta-analyses, one comparing LSG to LAGB and the other comparing LSG to LRYGB, were published in 2013 and are critically appraised below.

2.7.3.1 Wang et al. (2013). The purpose of this meta-analysis by Wang and colleagues (2013) was to compare the effects of LSG and LAGB on %EWL and T2DM. Searches for relevant publications from 2000 to 2012 were carried out via PubMed and Embase with the final search being conducted in August of 2012. Inclusion and exclusion criteria were well defined and a total of 11 studies consisting of a combined total of 1,004 patients were included in the meta-analysis. The included studies were a mixture of randomized and non-randomized studies. Of the 1,004 patients, 616 underwent LAGB and 388 underwent LSG. The length of follow-up in the studies included ranged from 6 to 12 months. Statistical heterogeneity was tested by the chi-square test and according to the forest plots, heterogeneity was limited and the Mantel-Haenszel fixed effect model was used.

The results of the meta-analysis indicated that LSG had a greater effect than LAGB on %EWL and was superior in treating T2DM at 6 and 12 months post-surgery. Five studies reported 42 of 68 patients (61.8%) living with T2DM experienced improvement of their diabetes after LAGB compared to 66 of 80 (82.5%) patients living with T2DM who improved following LSG. The authors concluded that LSG was a more effective procedure than LAGB, with a pooled odds ratio of 0.34 (95% CI 0.16-0.73).

One common limitation in meta-analyses is publication bias. While the authors produced a series of funnel plots to assess the publication bias of the literature it remains that searches were not inclusive of unpublished data, conference abstracts, or studies not in the English language. Secondly, there were a small number of studies included in the analysis, some of which had low sample sizes which may have biased the results. Also,

the papers included that studied LSG lack long-term results, with most reporting on 6 and 12 month data. Perhaps the most limiting factor of this meta-analysis is that the definition of improvement or remission of T2DM is not clearly stated in the paper. It is recommended that larger, randomized, long-term follow-up studies be conducted to compare the efficacy of LSG, LAGB, and LRYGB.

2.7.3.2 Li et al. (2013). The aim of this meta-analysis of randomized controlled trials (RCT) was to compare the efficacy of LRYGB and LSG in treating morbid obesity or T2DM. Searches for relevant RCTs in any language, published between 1966 and 2012 were carried out via Cochrane Central Registrar of Controlled Trials, Medline, Embase, ISI databases, and the Chinese Biomedical Literature Database. The authors had well-defined inclusion and exclusion criteria and a total of 5 RCTs were selected for inclusion in the meta-analysis. The quality of the included studies was assessed using the Jadad composite scale (range 0 to 5) which assesses randomization, blinding, and dropouts and all studies scored 4 or higher. These 5 RCTs encompassed a total of 396 patients; 196 patients in the LRYGB group and 200 in the LSG group. The length of follow-up in the studies ranged from 1 to 36 months with the majority (3) of the studies reporting a 12 month follow-up period. Remission of T2DM was defined as FPG levels less than 126 mg/dL (7.0 mmol/L) and A1c levels less than 6.5% without the use of antidiabetic medications. The studies were homogenous with respect to clinical and methodological criteria and the chi-square test statistic was used to assess any heterogeneity among the studies. Summary estimates were calculated using a fixed-effects model.

The results showed that the patients who underwent LRYGB lost more weight, had a higher remission rate of T2DM (OR 9.08, 95% CI 2.39-34.41, p=0.001), and had lower LDL, triglycerides, and insulin levels than those in the LSG group. Based on these results the authors concluded that LRYGB is more effective than LSG for the surgical treatment of T2DM; however, LSG is safer and has a lower rate of complications following surgery. It is also noted that LRYGB excludes the duodenum leading to long-term micronutrient deficiency in patients however this is avoided in LSG patients as that procedure does not exclude the duodenum. The authors recommend that in order to provide more reliable evidence, more high-quality RCTs with longer-term follow-up periods must be conducted.

One strength of this study was that the outcome measure for remission of T2DM was clearly defined by the authors. In terms of limitations, this meta-analysis was primarily limited by the lack of RCTs with large sample sizes and long-term follow-up. Small sample sizes could be the reason that the 95% CI (2.39-34.41) was so wide for the difference in the rate of remission of T2DM between patients who underwent LRYGB and LSG. Lack of long-term follow-up makes it almost impossible to comment on the durability of remission of T2DM post-surgery and the possibility of weight re-gain in the future.

2.7.4 LSG & Remission of T2DM. Current research indicates that while LRYGB appears to be a more efficacious procedure than LSG with respect to weight loss and T2DM remission, it is a much more complex surgical procedure associated with significant morbidity postoperatively (Gill et al., 2010; Li et al., 2013). LSG has been

reported to promote weight loss and improve T2DM remission rates; however, while meta-analytic techniques involving a large number of studies have been identified in the literature exploring the effectiveness of LSG in the setting of T2DM, the individual studies have small, heterogeneous patient populations (Gill et al., 2010; Li et al., 2013; Wang et al., 2013). A systematic review was conducted by Gill et al. in 2010 to review the effect of LSG on T2DM. The information from this systematic review has been combined with data from studies published between 2010 and 2014 with the baseline demographics presented in Table 2.4 and the results with respect to weight loss and T2DM remission presented in Table 2.5. A critical appraisal of this systematic review is presented below.

2.7.4.1 Gill et al. (2010). This study was carried out with the intention of systematically reviewing the existing literature on the efficacy of LSG for weight loss and the remission of T2DM. Studies between the years 2000 and April 2010 were identified using electronic databases such as MEDLINE, PubMed, Embase, Scopus, Dare, Clinical Evidence, BIOSIS Previews, TRIP, Health Technology Database, Cochrane Library, conference abstracts, and clinical trials. The authors also took into consideration unpublished and non-English language studies in an effort to reduce publication bias. Based on the inclusion criteria, 27 studies reporting data on a total of 673 patients were chosen to be included in the systematic review. Remission of T2DM was defined as discontinuation of all antidiabetic medications and normal FPG levels, normal postprandial glucose excursions, and normal A1c. The high heterogeneity among the

studies and a lack of RCTs deemed a meta-analysis to be inappropriate. Follow-up time in the studies ranged from 3-36 months with a mean follow-up time of 13.1 months.

Of the 27 included studies, 26 included the primary outcome of T2DM remission. Remission rates ranged from 14% to 100% with 20 studies reporting remission rates of T2DM ≥ 50%. A total of 19 studies also reported improvements in T2DM with the improvement rates ranging from 2% to 86%. It is still unknown if the LSG induced improvement in T2DM will translate into a long-term decrease in patient mortality.

At the time of the systematic review, no RCTs had been published assessing the remission of T2DM following LSG. However, the authors conducted a comprehensive review of the available literature and assessed the articles for methodologic quality using the Cochrane (concealment of allocation) and risk of bias tools. There are numerous potential sources of bias inherent in non-randomized studies, thus the results of this systematic review should be interpreted with caution. The authors indicate a need for the development of high-level randomized clinical trial evidence on this issue.

Based on the results, the authors concluded that LSG has a substantial effect on T2DM with most patients experiencing remission of T2DM following surgery. The authors promoted LSG as a promising surgical procedure for the treatment of obesity and T2DM.

Table 2.4

Baseline Characteristics of Studies Included in the Systematic Review and Recent Studies***

Investigator	**Patients (n)**	**Mean Age (years)**	**Gender (% Female)**	**Mean BMI (kg/m^2)**	**Follow-up period (months)**
Sieber et al., 2014**	68	43.1	78	43.0 ± 8.0	60
Perathoner et al., 2013**	93	46 (median)	73	44.1 ± 6.9	17.4 (mean)
Desiderio et al., 2013**	15	58.8	67	37.9 ± 1.5	12
Rawlins et al., 2013**	49	44	70	65	60
Abbatini et al., 2013**	26	49.3	70	52.1 ± 8.5	36
Slater et al., 2011**	22	55.3	21	46	12
Lakdawala et al., 2010*	7				12
Lirosi et al., 2010*	34		68	53 ± 8	3
Nienhuijs et al., 2010*	20	42		51	12
Sammour, et al., 2010*	25				12
Shah et al., 2010*	53	46.5 ± 8.7	55	45.2 ± 9.3	12
Todkar et al., 2010*	23	44.6 ±11.9	74	40.7 ± 6.6	36
Basso et al., 2009*	20	46.6 ± 4.2	60	51.6 ± 16	36
Berry et al., 2009*	14	50.6 ± 12.7	64	38.3 ± 6.7	6
Chowbey et al., 2009*	23				6
Frezza et al., 2009*	53	51	79	53.5	18
Jacobs et al., 2009*	39				12
Keidar et al., 2009*	18				3
Letessier et al., 2009*	18				14
Magee et al., 2009*					12
Nocca, 2009*	33			50.6	12
Rosenthal et al., 2009*	30	42.3	70	46.1 ± 11	6
Cottam et al., 2006*	75				12
Gan et al., 2007*	21		62	52.8 ± 8.2	11.4
Kasalicky et al., 2008*	17				18
Lee et al., 2008*	20	46.3	70	31 ± 2.9	12
Ou Yang et al., 2008*	33			50.6 ± 11	24
Tagaya et al., 2008*	6				12
Vidal et al., 2008*	39	49.9 ± 1.5	59	51.9 ± 1.2	12
Wheeler et al., 2008*	13				3.4
Weiner et al., 2007*	14				12
Moon Han et al., 2005*	8				6
Silecchia et al., 2005*	17				18

Note: BMI= Body Mass Index, PCS= Prospective Clinical Study, RCS= Retrospective Clinical Study, RCT= Randomized Clinical Trial.

Table 2.5

Laparoscopic Sleeve Gastrectomy Outcomes for Studies Included in the Systematic Review and Recent Studies***

Investigator	Glucose level (mmol/L)		A1c (%)			%EWL	T2DM (%)		
	Pre	Post	Pre	Post	Change (%)		Resolved	Improved	Stable
Sieber et al., 2014**							85		
Perathoner et al., 2013**			5.9	5.4	-0.45	55.7	85		
Desiderio et al., 2013**	9.91	6.26	8.1	5.6	-2.5	58.4	40	33.3	26.7
Rawlins et al., 2013**						86.0	100		
Abbatini et al., 2013**	7.95	4.91	7.3	5.5	-1.8		85		
Slater et al., 2011**			7.4	6.1	-1.3	56	75	25	
Lakdawala et al., 2010*							98	2	
Lirosi et al., 2010*						6.3	85	15	
Nienhuijs et al., 2010*						49.6	50	40	10
Sammour, et al., 2010*							48	24	7
Shah et al., 2010*			8.4	6.1	-2.3		96.2	3.8	
Todkar et al., 2010*	8.74	5.38	9.1	6.4	-2.7	74.6	69.6		30.4
Basso et al., 2009*			7.7	5.9	-1.8	36.3	80.9		
Berry et al., 2009*	7.33	5.37	7.1	5.5	-1.6		85.7	14.3	
Chowbey et al., 2009*			6.46	5.2	-1.26		82.6	17.4	
Frezza et al., 2009*		6.55				59.2			
Jacobs et al., 2009*							82	18	
Keidar et al., 2009*							77		
Letessier et al., 2009*							41.2	47.1	
Magee et al., 2009*							23		
Nocca, 2009*						60.1	75.8	15.2	
Rosenthal et al., 2009*	8.82	7.12	6.4	5.9	-0.5	35.4	63.3	36.7	
Cottam et al., 2006*						46	81	11	
Gan et al., 2007*	8.09	5.79	8	6.6	-1.4	35.9	14	81	5
Kasalicky et al., 2008*							71	29	
Lee et al., 2008*	13.33	7.38	10.1	7.1	-3.0	70.4	50		
Ou Yang et al., 2008*			7.91	6.47	-1.44	46.1	39		
Tagaya et al., 2008*							67	33	
Vidal et al., 2008*	14.03	8.72	7.4	6.9	-0.5		84.6		
Wheeler et al., 2008*					-2.2		61.5		
Weiner et al., 2007*							14	86	
Moon Han et al., 2005*							100		
Silecchia et al., 2005*							79.6	15.4	

Note: %EWL= Percent Excess Weight Loss, A1c= Glycated Hemoglobin, T2DM= Type 2 Diabetes Mellitus; case definitions of remission and improvement vary

2.7.5 How Does LSG Work? Conventionally, it is thought that weight loss and remission of T2DM following LSG results directly from gastric and caloric restriction after anatomically reducing the size of the stomach. However, there is growing evidence to suggest that these mechanisms are not the primary driving force behind metabolic improvements post-surgery. Below are some proposed mechanisms of weight loss and T2DM remission following LSG.

One hypothesis that is gaining popularity is that weight loss and metabolic improvements after LSG occur following changes in gut physiology leading to changes in hormone production, for example, ghrelin and peptide-YY (PYY). Ghrelin is produced by endocrine cells in the fundus of the stomach and functions to increase appetite and promote gastric emptying and intestinal mobility inducing feelings of hunger (Xanthakos, 2008). A study by Langer et al. (2005) reported that ghrelin levels following LSG were reduced as early as one day post-surgery and ghrelin levels remained low and stable at 1 and 6 months follow-up which is likely due to the resecting of the fundus of the stomach during LSG. Thus, patients have less appetite for food and a longer-lasting sensation of fullness leading to decreased food intake and weight loss following LSG. A second hormone, PYY also plays an important role in weight loss. PYY is produced in the distal ileum and colon and has a hunger-reducing effect (Wang et al., 2013; Xanthakos, 2008). Research indicates that postprandial PYY levels increase following LSG which further increases the weight loss effects of LSG (Karamanakos et al., 2008). It may be that the combination of reduced gastric volume and hormonal changes seen after LSG contribute

to the greater weight loss achieved following LSG compared to LAGB (Wang et al., 2013).

With respect to improvements in T2DM it is believed that by countering insulin resistance brought on by severe obesity with increased insulin sensitivity, improved control of T2DM can be achieved (Wang et al., 2013). Any bariatric procedure which induces weight loss will increase insulin sensitivity and thereby improve T2DM; however, it is still uncertain if weight loss is the major contributor to improvement of T2DM following LSG.

Incretins such as GLP-1 and GIP also play an important role in the improvement of T2DM and weight loss. GLP-1 is secreted in the ileum and colon and increases pancreatic secretion of insulin in response to oral glucose ingestion to decrease serum levels of glucose. It is thought that GLP-1 increases following LSG which further helps to ameliorate T2DM (Wang et al., 2013). The hormonal changes that occur paired with the weight loss induced by LSG may be the contributing factors to the remission of T2DM post-surgery.

Given that a substantial number of patients living with T2DM are no longer taking antidiabetic medications within days after bariatric surgery and before substantial weight loss has occurred, new hypotheses are emerging to try and explain this phenomenon. Recently, a paper published by Ryan et al. (2014) hypothesized that the effects of LSG on weight loss and improved glucose control were related to bile acids. In addition to aiding mechanical digestion and absorption of lipids, bile acids regulate metabolism by binding

to the nuclear receptor farsenoid-X receptor (FXR). LSG is one bariatric procedure that is associated with significantly higher levels of circulating total bile salts in human and rodent models. The authors examined the effects of LSG on mice with diet-induced obesity and targeted genetic disruption of FXR. In this study, LSG was associated with a 20% decrease in fasting blood glucose and substantial improvements in glucose tolerance in unaltered mice whereas mice with genetic disruption of FXR experienced an increase of 24% in fasting blood glucose levels and exhibited no changes in glucose tolerance post-surgery. These results indicate that in the absence of the nuclear receptor FXR, the ability of LSG to reduce body weight and improve glucose tolerance is reduced substantially.

Furthermore, FXR was shown to alter feeding behaviors following LSG (Ryan et al., 2014). When given the choice between three diets, mice with no disruption in FXR that underwent LSG exhibited a preference for dietary carbohydrates and protein relative to dietary fat and maintained a lower food intake for up to 3 weeks, neither of which was the case in mice with genetic disruption of FXR (Ryan et al., 2014). This indicates that increased levels of bile salts, along with natural changes in dietary preferences may be responsible for weight loss and comorbid resolution following LSG.

However, the physiology of bile acids is different between mice and humans so caution should be exerted when translating these results to humans (Kuipers & Groen, 2014). This finding by Ryan et al. (2014) should encourage future studies to try and explain the mechanism by which FXR influences the metabolic effects of LSG and comparable procedures in humans (Kuipers & Groen, 2014).

While many hypotheses exist, the exact mechanism by which LSG induces weight loss and metabolic improvements is still uncertain. With LSG being a relatively new procedure compared to other bariatric surgeries, more studies are necessary to determine the exact mechanism or combination of mechanisms that work together to provide the weight loss and metabolic benefits following this procedure.

2.7.6 Remission of Type 2 Diabetes Mellitus: Definition & Predictors. With the concepts of "remission" and "cure" of T2DM following bariatric surgery gaining acceptance, it is necessary to define what these terms mean in the case of diabetes. Improved or normalized glycemic levels are obvious factors to be considered but is it appropriate to use the term remission or cure for all patients with normal glycemic measures irrespective of how this is achieved? In 2009, a consensus group comprised of experts in pediatric and adult endocrinology, diabetes education, transplantation, metabolism, bariatric/metabolic surgery, and hematology-oncology was formed to discuss this issue. For a chronic disease such as diabetes, it is more appropriate to use the term remission rather than cure due to the likelihood that any current or potential treatments for T2DM will likely leave patients at risk for relapse as a result of underlying pathophysiologic abnormalities and/or genetic predisposition to the disease. The consensus group agreed upon using various stages of remission in their definition of remission of diabetes (Table 2.6). It is also noted that the specific (microvascular) or nonspecific (cardiovascular) complications patients can experience as a result of living with diabetes will likely need ongoing monitoring indefinitely even if a patient achieves prolonged remission of diabetes (Buse et al., 2009).

Table 2.6

*Summary of Consensus Group Definitions of Remission of Type 2 Diabetes Mellitus**

Partial Remission
Glycemic measures above normal but below diagnostic thresholds for T2DM
At least 1 year's duration
No active pharmacologic therapy
Complete Remission
Normal glycemic measures
At least 1 year's duration
No active pharmacologic therapy
Prolonged Remission
Complete remission of at least 5 years' duration

*Buse et al., 2009

Research has been conducted to determine if there are any preoperative prognostic factors that can be used to predict the likelihood of a patient achieving remission of T2DM following bariatric surgery. A study by Casella et al. (2011) looked specifically at ten-year duration of T2DM as a prognostic factor for remission following sleeve gastrectomy. The study reported that the duration of T2DM was an important prognostic factor with patients living with T2DM for less than 10 years experiencing 100% remission while those patients living with T2DM for more than 10 years experiencing significantly lower rates of remission. Robert et al. (2013) conducted a study aimed at identifying predictive factors of T2DM remission one year after bariatric surgery and found that baseline BMI < 50 kg/m^2, duration of T2DM ≤ 4 years, A1c ≤ 7.1%, FPG < 6.3 mmol/L, and absence of insulin therapy were predictors of remission of T2DM. Research carried out by Still et al. (2013) aimed to create a score to predict remission of T2DM which took into account preoperative insulin use, age, A1c concentration, and type of antidiabetic drugs being used in predicting the likelihood of a patient achieving remission of T2DM post-surgery with the greatest weight given to insulin use before surgery. A final study conducted by Lee et al. (2013) reported that operative methods, waist circumference, and C-peptide levels were significant predictors for the remission of T2DM following bariatric surgery. These four studies report a variety of potential prognostic factors that can predict a patient's likelihood of achieving remission of T2DM. More research on this topic is necessary to determine which of these factors are the best predictors of remission and which factors are of the most importance before it is possible to use this information as a means of recommending candidates for surgery to achieve remission of T2DM.

The above factors that are mentioned as being predictive of remission of T2DM following bariatric surgery are indicators of decreases in pancreatic islet cell reserve. Declining islet cell function begins as early as 12 years prior to diagnosis of T2DM with the acute insulin response decreasing by 27% during the progression from normal to impaired to glucose tolerance, and by 51% during the transition from IGT to T2DM (Fonseca, 2009). This helps explain duration of diabetes, age, blood glucose levels, and insulin use as potential predictors of remission of T2DM. The remaining predictive factor, C-peptide level, is a direct measure of islet cell reserve as C-peptide is cleaved from proinsulin in order to release mature insulin; thus, low levels of C-peptide in diabetic patients are indicative of decreased islet cell function or reserve (Wahren et al., 2000).

Research is not only focused on preoperative prognostic factors of remission of T2DM following bariatric surgery but also on the prevention of T2DM following surgery. A study by Carlsson et al. (2012) investigated the effect of bariatric surgery on the prevention of T2DM. This nonrandomized, prospective, controlled study included 3429 patients; 1658 patients underwent bariatric surgery and 1771 obese matched controls. After a 15 year follow-up period, T2DM developed in 392 patients in the control group and in 110 bariatric surgery patients. The corresponding incidence rates of T2DM were 28.4 cases per 1000 person-years for the control group and 6.8 cases per 1000 person-years for the surgery group (adjusted hazard ratio with bariatric surgery, 0.17, 95% CI 0.13-0.21, $p<0.001$). The effect of bariatric surgery on incident T2DM was influenced by the presence or absence of IFG but not by BMI. The authors concluded that bariatric

surgery was markedly more efficient than usual care in the prevention of T2DM in obese persons.

2.8 Summary of Gaps in the Clinical Literature

A review of the clinical literature revealed several gaps that exist in current knowledge related to bariatric surgery and the improvement or remission of T2DM. Firstly, there are very limited data available on outcomes following LSG from a Canadian health care perspective. Secondly, none of the studies explored the effects of bariatric surgery on the improvement of glycemic control in patients living with prediabetes. Prediabetes is a major risk factor for the development of T2DM, thus if bariatric surgery is successful in ameliorating prediabetes then the incidence of future diabetes in this at-risk population will decrease. Finally, despite the fact that in 2009 Buse and colleagues released guidelines specifically outlining definitions of remission for T2DM there is still major heterogeneity amongst existing studies when defining T2DM remission. These gaps in the literature provided the basis of the present research and helped guide the development of the research questions.

Chapter 3: Methods

This chapter outlines the study population and sample, procedure, definitions of the outcomes of interest, data analysis, and ethical considerations. A standardized data abstraction form was used to collect the following information: patient demographics such as age, gender, employment status, level of education, history of comorbid conditions, etc.; weight, height; blood glucose levels, cholesterol, triglycerides, blood pressure; and medication use. The statistical data analysis plan used to answer the research questions and ethical considerations are also discussed. This research was conducted using a prospective, inception cohort study design.

3.1 Population and Sample

The eligible population for this inception cohort study was all individuals who underwent LSG in NL between May 2011 and September 2013 and consented to participate in the NL BaSco Study. This time period was chosen so that, at the time of analysis, all patients included in the analysis would have been eligible for at least a six month follow-up appointment. The sample consisted of patients who, before undergoing surgery, met the following inclusion criteria: (a) based on laboratory results met the requirements for a case diagnosis of prediabetes, FPG level of 6.1 mmol/L - 6.9 mmol/L or A1c level of 6.0% – 6.4% (Goldenberg & Punthakee, 2013); or (b) based on laboratory results, met the requirements for a case diagnosis of T2DM, FPG $\geq$ 7.0 mmol/L or A1c $\geq$ 6.5% (Goldenberg & Punthakee, 2013); and/or (c) a self-reported history of impaired fasting glucose or diabetes, or were taking antidiabetic medications at baseline. The

antidiabetic medications included in this study are biguanide (metformin), sulfonylureas (gliclazide, glyburide), alpha glucosidase inhibitor (acarbose), dipeptidyl-peptidase-4 (DPP-4) -inhibitors (saxagliptin, sitagliptin), meglitinides (repaglinide, nateglinide), thiazolidines (pioglitazone, rosiglitazone), glucagon-like-peptide-1 (GLP-1) receptor aganosits (liraglutide), rapid-acting insulin (insulin lispro, insulin aspart), fast-acting insulin (regular insulin), intermediate-acting insulin (insulin NPH), and long-acting insulin (insulin glargine, insulin detemir).

At the end of September 2013, 171 individuals had undergone LSG. Of these patients, 24 (14.0%) were defined as having prediabetes and 67 (39.2%) were defined as having T2DM before undergoing surgery.

3.2 Procedure

For this study, data was collected from the time surgery began in the province in May 2011 until March 2014 (i.e., during the pre-admission process and at various time intervals after surgery). Patients were referred by their family physician to the provincial bariatric surgery program housed in the Health Sciences Center at Eastern Health, the province's tertiary care center, where the bariatric nurse practitioner performed a preliminary eligibility screening of patients and invited eligible patients to a pre-surgical education session. Information regarding the surgical procedure, the importance of nutrition, and how to read food product labels was provided at this session. Patients were encouraged to start a food journal and initiate a daily multivitamin regime. Following the education session, interested patients met with the bariatric nurse practitioner and a detailed medical history was taken. Once deemed eligible for surgery, patients were

informed of the research study by a member of the clinical team and permission was requested for a research nurse coordinator to meet with them to provide more information. The research nurse gave each potential participant a detailed explanation of the study, an introductory letter addressed from the researcher and a consent form at their initial clinic visit with the nurse practitioner. Permission was obtained to meet again after their scheduled appointment with the surgeon to review the research project after the potential participant had at least 24 to 48 hours to review the materials. Once the surgeon gave final approval for LSG and obtained written surgical consent, the research nurse met with the potential participant to answer any questions and obtain informed written consent to participate in the cohort study.

Baseline data was collected after informed consent was given. For this analysis, 172 patients were approached by the research nurse to participate in the study and 171 agreed to participate giving a response rate of 99.4%. For the purposes of the current thesis, the sample size is n=171. A diagram outlining the pre-surgical process for patients from the time of referral to the date of surgery is presented in Figure 3.1.

Laboratory assessments were completed throughout the province but the majority of the biochemical assessments were performed at the Health Sciences Centre in St. John's. The methods and equipment used to perform the biochemical assessments were obtained through personal correspondence with Dr. Edward Randell, Division Chief, Department of Laboratory Medicine, Eastern Health. The analysis for FPG, triglycerides, HDL, and cholesterol were performed on the Architect c8000 and c16000 clinical chemistry systems by Abbott Diagnostics. A1c values were analyzed on a G8 HbA1c

analyzer (Tosoh) by HPLC. Values of LDL were calculated using the Friedewald equation. In all cases, the necessary testing reagents came from the same vendors as listed above.

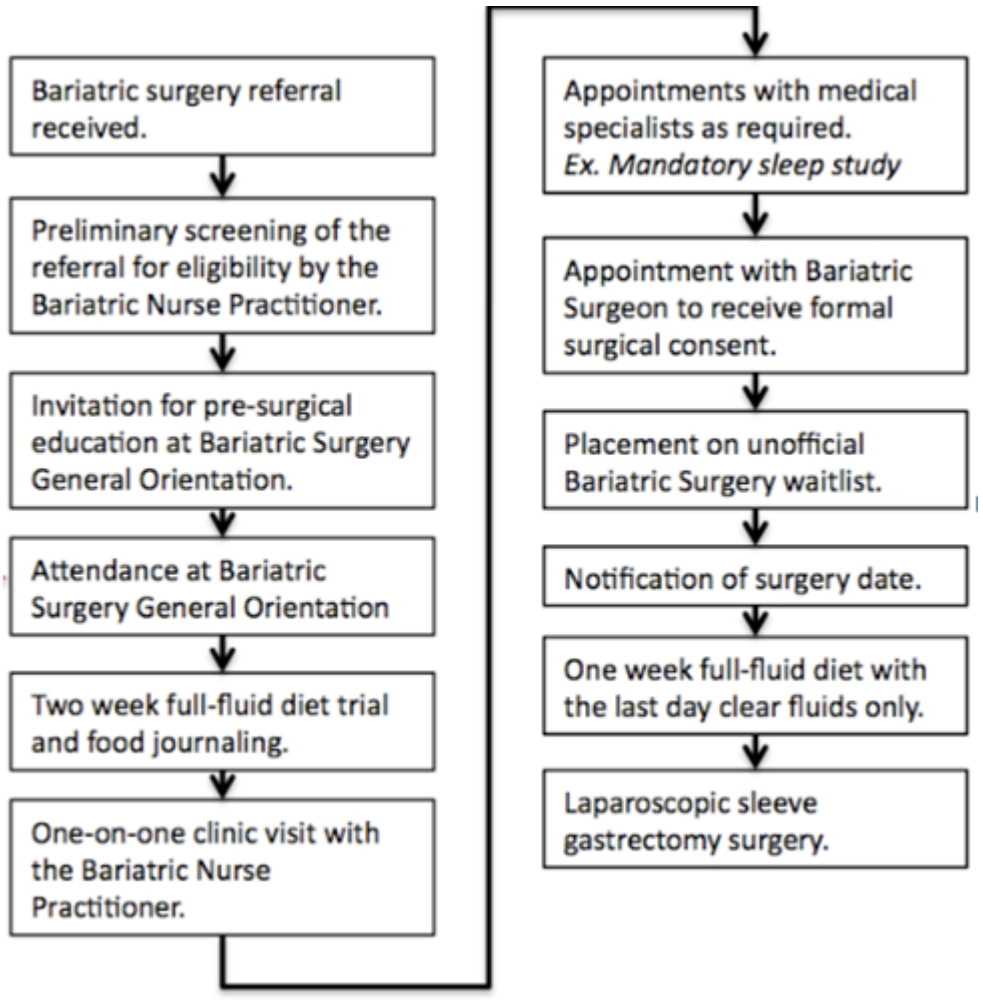

Figure 3.1. **The pre-surgical process for patients from referral for bariatric surgery to undergoing laparoscopic sleeve gastrectomy.**

After consenting to participate in the study, patients filled out a series of questionnaires to collect information on socio-demographics, health services use, and quality of life. For one week prior to surgery, patients were required to follow a full-fluid diet. This diet was fully outlined for the patients by the dietician and the daily recommendations were as follows: fluid intake of 2-3 litres for females or 3-4 litres for males, protein supplements of 60-80 grams, calorie intake of 800-1200 kcal, and an adult multivitamin-mineral supplement. Patients recorded their daily food intake during the week which was later reviewed by the dietician. The full fluid diet was resumed again after surgery for a period of 4 weeks after which soft foods were re-introduced into the diet followed by solid foods 8 weeks post-surgery. As part of clinical standards of care and following the full fluid diet, patients had standard blood work completed at the pre-admission clinic. Patients' official pre-surgery weight, blood pressure, heart rate, and waist circumference, and medication use were also recorded at the pre-admission clinic.

Follow-up appointments took place at 1, 3, 6, and 12 months post-surgery. The 1 month appointment was a clinic visit with the bariatric nurse practitioner where anthropometric measures, blood pressure, heart rate, and medication use was recorded. At every other follow-up appointment, blood work was required to be completed and medication use recorded. Questionnaires regarding health services use and quality of life were re-administered at 6 and 12 months post-surgery.

3.3 Defining Primary Outcome Measures of Prediabetes & T2DM

Following data entry, it was necessary to determine if, at baseline, patients had normal glucose tolerance, type 1 diabetes, prediabetes, or T2DM; the latter two being the

focus of the current research study. Depending on the relationship that a patient has with their family physician, the patient may or may not have regular blood testing done. It is for this reason that we could not fully rely on a patient's self-reported medical history to determine if they were prediabetic or had T2DM. The process of identifying prediabetic or T2DM patients is outlined in sections 3.3.1 and 3.3.2, respectively and begins with examining the results from the laboratory testing. Patients with FPG and A1c levels in the normal range, with no reported history of IFG, diabetes, or antidiabetic medication use were considered to have normal glucose tolerance. Patients with type 1 diabetes (n=1) were identified by the bariatric nurse practitioner on the medical history form and recorded appropriately in the database and were not included in the current analysis.

3.3.1 Prediabetes. Prediabetes, as outlined in Chapter 2, is defined as FPG levels ranging from 6.1–6.9 mmol/L and A1c levels from 6.0–6.4%. Thus, the first step in identifying prediabetic patients was to examine their blood glucose levels. Any patient with FPG and/or A1c levels within this range was further investigated. The next step was to consider the patient's medication use. If the patient was not taking medication for diabetes s(he) was coded as prediabetic. If the patient was taking antidiabetic medications the medication dose was taken into consideration. In 2 cases where it was uncertain whether or not the patient was prediabetic or had T2DM another member of the research team with expertise in endocrinology was consulted (CK).

3.3.2 T2DM. The case definition of T2DM is FPG $\geq$ 7.0 mmol/L or A1c $\geq$ 6.5% thus, any patient with glucose levels above these thresholds was considered to have T2DM. Other patients whose diabetes was medically managed were identified through

their medication use profile as well as their self-reported medical history. Patients' glycemic control and medication use was re-evaluated at 3, 6, and 12 months post-surgery. Only medication use was recorded at the 1 month appointment. No laboratory testing was completed at that time.

3.3.3 Case Definitions of Improvement and Remission of Prediabetes and T2DM. Case definitions of improvement or remission of prediabetes and T2DM were created based on the recommendations by Buse et al. (2009) and are presented in Table 3.1 and Table 3.2, respectively. Definitions take into consideration glycemic levels (i.e., FPG, A1c) as well as any changes in the use of antidiabetic medications post-surgery.

Table 3.1

Case Definitions of Improvement and Remission of Prediabetes

Improvement
Lower glycemic measures
At least 1 year's duration
Pharmacologic therapy required but at a lower dose
Normalization
Normal glycemic measures
At least 1 year's duration
Pharmacologic therapy required but at a lower dose
Remission
Normal glycemic measures
At least 1 year's duration
No active pharmacologic therapy

Table 3.2

*Case Definitions of Improvement and Remission of Type 2 Diabetes Mellitus**

Improvement
Hyperglycemia below diagnostic thresholds for T2DM
At least 1 year's duration
Pharmacologic therapy required but at a lower dose
Partial Remission
Hyperglycemia below diagnostic thresholds for T2DM
At least 1 year's duration
No active pharmacologic therapy
Complete Remission
Normal glycemic measures
At least 1 year's duration
No active pharmacologic therapy

*Buse et al., 2009

3.4 Data Analysis

Data was entered into Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM Corp., Armonk, NY) for analysis. Data quality assurance was carried out using descriptive statistics and frequencies. There were no apparent errors related to data entry and no outliers were identified. This research is part of a larger study that is using a prospective cohort design to assess short-term outcomes (e.g., weight loss, improvement/remission of T2DM, health care use and costs) in patients undergoing LSG.

3.4.1. Baseline Demographics. Descriptive statistics were used to create a profile of participants' personal characteristics, anthropometric measures at baseline, comorbidity status, biochemical parameters, and medication use. Based on the inclusion criteria, the percentage of patients with prediabetes or T2DM was also calculated.

3.4.2. Analysis of the Primary Outcomes. The primary outcomes for this study were the determination of the proportions of patients experiencing improvement or remission of prediabetes or T2DM as well as if any changes occured in FPG or A1c levels 12 months following LSG. The proportion of patients that achieved remission of prediabetes or T2DM 12 months after surgery were reported as frequencies and percentages based on the case definitions presented in Tables 3.1 and 3.2, respectively.

To determine if any changes in FPG and A1c levels were statistically significant, data were analyzed using Generalized Estimating Equation (GEE) regression models. GEEs represent an extension of the generalized linear model of continuous, ordinal, polychotomous, dichotomous, and count-dependent data which are designed to

accommodate for correlations between repeated measures (Twisk, 2003). Data for FPG and A1c levels were collected at baseline and at three time points post-surgery (3, 6, and 12 months) making this data repeated measures. It was inappropriate to conduct repeated measures ANOVA analysis on this data as many patients were missing information at various time points and would thus be excluded from the statistical analysis. GEE was used so that all patients could be included in the statistical analysis as this method does not assume that there is complete information for every patient and adjusts for correlations between measurements which exist in this data as they are repeated measures. The model used a normal linear link function, had a normal outcome distribution, and an exchangeable correlation structure. Time was included as a factor in the model and baseline values were used as the comparator in order to assess if there was a statistical difference in changes of FPG and A1c levels at 3, 6, and 12 months post-surgery. Statistical significance was set at $p<0.05$ using the Wald chi-square test carried out in the GEE analysis.

3.4.3 Analysis of the Secondary Outcomes. The analysis of the secondary outcomes focused on the examination of any associations between baseline factors, or change in weight 12 months post-surgery and remission of prediabetes or T2DM. Changes that occurred in weight and other variables including blood pressure, fasting lipid panel levels and triglycerides, and dose and number of antidiabetic medications prescribed 12 months post-surgery were also investigated.

The strength and direction of relationships between baseline factors or change in weight and remission of prediabetes or T2DM were established through the use of the

Pearson product moment correlation (Pearon's *r*) or its non-parametric equivalent Spearman's rho when determining the correlation between two continuous variables or Fisher's exact test when determining the association between two categorical variables. The variables chosen to be included in the analysis were based on the baseline information collected from patients and previously published research examining predictors of remission of T2DM following bariatric surgery.

Based on previously published research, baseline BMI, pre-operative insulin use (Robert et al., 2013), and age (Still et al., 2013) were chosen to be included in the univariate association analysis. Baseline weight was included as it has been thought to potentially be indicative of remission of diabetes (Lee et al., 2013). Levels of triglycerides were included as decreases in triglyceride levels can often be predictive of improvements in insulin resistance (Ginsberg et al., 2005); thus, if triglyceride levels decreased post-surgery it would be interesting to see if these changes were associated with remission of T2DM. Sex was included to explore whether or not females were more likely to experience remission of T2DM than males or vice versa. Finally, self-reported medical histories of hypertension, dyslipidemia, and in the T2DM cohort chronic renal disorder, were chosen because these are common comorbidities associated with diabetes and may be indicative of more advanced diabetes in a patient; thus, it was interesting to see if patients with or without these conditions were more likely to achieve remission of prediabetes or T2DM 12 months post-surgery.

Averages of weight, blood pressure, fasting lipid panel levels and triglycerides were calculated at baseline and at 3, 6, and 12 months post-surgery. Changes in these

variables were calculated as differences between the pre- and post-surgery values. Statistical significance of any changes in these values was determined using GEE as was done for the primary outcome. The model was set-up in an identical manner for each of these outcomes.

Percent excess weight loss (%EWL) is defined as the percentage of excess weight a patient loses post-surgery and was calculated based on the equation: %EWL = (initial weight – weight at follow-up) ÷ (initial weight – ideal body weight) x 100 (Picot et al., 2009). Ideal body weight was determined using the mean of the medium frame ideal body weights for men and women based on height from the 1983 Metropolitan Height and Weight Tables (1983 metropolitan height and weight tables, 1983). An equation to illustrate the concept of %EWL is provided: a female patient with a height of 5'3" and weight of 240 lbs has a BMI of 42.7. She would have an ideal BMI of 25 if she weighed 140 lbs meaning she carries 100 lbs of excess weight. Following LSG, she can expect to lose between 45-60% of her excess weight. Thus, post-surgery, she can expect to lose anywhere from 45-60 lbs putting her at a weight between 180-195 lbs.

Percent absolute weight loss (%AWL) is defined as the percentage of initial weight a patient loses post-surgery. The calculation of %AWL following surgery was based on the equation: %AWL = (initial weight – weight at follow-up) ÷ (initial weight) x 100.

Antidiabetic medication and statin use were reported as frequencies at each time point to represent the number of patients taking each medication and the dose of

medication was reported as an average value. The use of statins was included to aid in the discussion of any changes that may have occurred in HDL, LDL, triglycerides, and total cholesterol post-surgery.

3.5 Privacy & Ethical Considerations

Ethical approval and subsequent renewals for this research have been obtained from Memorial University's Health Research Ethics Authority (previously the Human Investigation Committee, HIC# 11.101). A copy of this approval can be found in Appendix A.

Patients were provided with written material describing the study and what would be expected of them for their own personal review before signing written, informed consent with the research nurse. Prior to signing consent, patients were made aware that they could choose to withdraw from the study at any time and were informed that all personal information would remain confidential and anonymous. All data was de-identified by the research nurse and each patient was given a unique ID to ensure anonymity of the participants to the research staff. All data was stored in a filing cabinet in the Patient Research Centre and electronic versions of the databases were stored on a password-protected computer. Only the research nurse had access to the master list; the anonymous questionnaires and access to the databases was limited to the primary investigators and research staff.

Data collected by the bariatric nurse practitioner and the research nurse were forwarded in a de-identified manner to another member of the research team (KL) for

entry into the database. Once the data abstraction form was received, it was photocopied, coded, and the data was entered into the database. The original abstraction form was returned to the research nurse for storage while the copy was stored in the Patient Research Centre in a locked cabinet. The computer containing the databases was password-protected and all files were backed up to an external hard drive as they were updated.

Chapter 4: Results

The following chapter presents the results of the study in 6 sections. The first section describes the demographic profile of the sample as well as for the prediabetes and T2DM cohorts including weight measures, comorbidity profile, and socio-demographic characteristics and laboratory measures. The second and third sections present the results for the prediabetes and T2DM cohorts, respectively including the proportion of patients that achieved improvement or remission of prediabetes as well as changes in glycemic measures post-surgery. The fourth section examines if there are any pre-operative factors that may be associated with the remission of prediabetes or T2DM following LSG. The fifth section examines if weight loss 12 months post-surgery was associated with changes in glycemic measures, triglycerides, fasting lipid panels, or remission of prediabetes or T2DM. The sixth section presents the results for the secondary research questions including changes in weight, BMI, blood pressure, and serum levels of triglycerides and cholesterol, and antidiabetic medication use post-surgery. It also presents changes in the use of statins post-surgery for the T2DM cohort. As previously noted, this research is part of a larger study that is using a prospective cohort design to assess short-term outcomes (e.g., weight loss, improvement/resolution of diabetes, health care use and costs) in patients undergoing LSG; thus, the analysis is based on a sample of patients from the population enrolled in the NL BaSco Study.

4.1 Baseline Demographics, Comorbidity Profile, & Laboratory Values

Of the 171 patients who had undergone LSG by the end of September 2013, 91 (53.2%) met the case definition for either prediabetes or T2DM. Figure 4.1 details the

number of patients included the study and breaks down the prediabetes and T2DM cohorts to show the number of patients returning at each follow-up period. The baseline characteristics are presented in Table 4.1. The study sample was predominantly female (76.9%) with an average age of 45.6 ± 10.4 years. The average weight was 135.6 ± 23.9 kg corresponding to an average BMI of 48.6 ± 7.1 kg/m^2. The average blood pressure before surgery was 130/80 ± 13/10 mmHg. The majority of the sample was Caucasian (90.1%) and either married or living in a common-law relationship (71.4%). The majority of the sample (64.8%) had received post-secondary education. Prior to surgery, in conjunction with the bariatric nurse practitioner, patients self-reported their medical history. The most commonly reported comorbidities were hypertension (67.8%), diabetes (62.8%), sleep apnea (61.6%), and dyslipidemia (60.5%).

Based on the case definitions outlined in Chapter 3, 24 patients (26.4%) were identified as prediabetic and 67 patients were identified as having T2DM (73.6%). Of the 67 patients identified as being diabetic 54 patients (80.6%) had a self-reported history of diabetes. Table 4.1 highlights the socio-demographic and anthropometric measures for each of these cohorts, as well as a detailed comorbidity profile. The cohorts do not differ significantly ($p<0.05$) in age, weight, BMI, blood pressure, or any of the socio-demographic factors. The proportions of patients in the T2DM cohort reporting a history of diabetes, dyslipidemia, or polycystic ovarian syndrome were statistically significantly ($p<0.05$) higher than the proportions of patients in the prediabetes cohort.

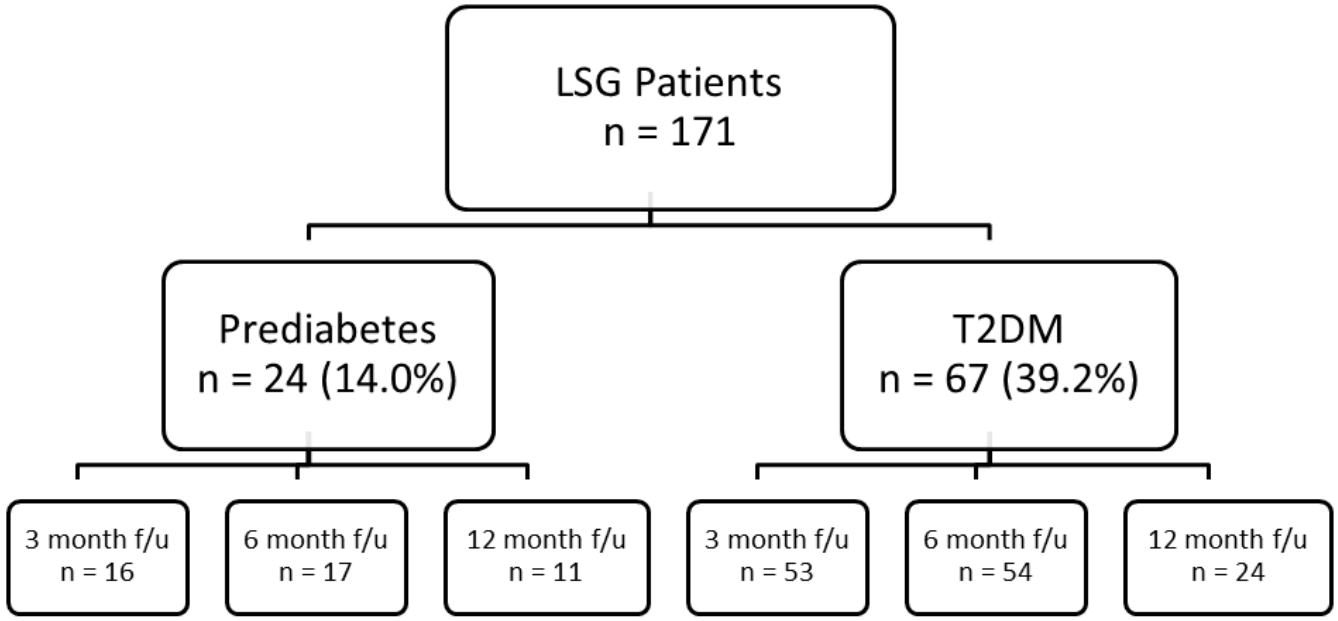

Figure 4.1. **Patients who had undergone LSG by the end of September 2013 divided into prediabetes and T2DM cohorts and their attendance of follow-up appointments.** f/u=follow-up, LSG=laparoscopic sleeve gastrectomy, T2DM = type 2 diabetes mellitus

Table 4.1

Baseline Demographics

Characteristic **Mean ± SD**	**All Patients (n=91)**		**Prediabetes (n=24)**		**T2DM (n=67)**	
Age, years	45.6 ± 10.4		46 ± 11.0		45 ± 10.4	
Weight, kg	135.6 ± 23.9		126.6 ± 22.9		138.8 ± 23.6	
BMI, kg/m^2	48.6 ± 7.1		46.7 ± 7.1		49.3 ± 7.0	
Blood Pressure, mm Hg						
Systolic	130 ± 13		131 ± 12		129 ± 14	
Diastolic	80 ± 10		83 ± 9		79 ± 10	
	n	**%**	**n**	**%**	**n**	**%**
Female	70	76.9	19	79.2	51	76.1
Caucasian	82	90.1	20	83.3	62	92.5
Married/Common-Law	65	71.4	16	66.7	49	73.1
Level of Education						
High School	14	15.4	6	25.0	8	11.9
College Diploma	40	43.9	8	33.3	32	47.8
University Degree	19	20.9	5	20.8	14	20.9
Other	18	19.8	7	29.2	22	32.8
Self-Reported Medical History[†]						
Hypertension	59	67.8	15	68.2	44	67.7
Diabetes*	54	62.8	2	9.5	52	80.0
Sleep Apnea	53	61.6	13	59.1	40	61.5
Dyslipidemia*	52	60.5	9	40.9	43	67.2
Osteoarthritis	41	47.7	10	45.5	31	47.7
Polycystic Ovarian Syndrome*	19	27.1	1	5.2	18	35.3
Hypothyroidism	16	18.6	2	9.1	14	21.5
Chronic Renal Disorder	8	9.3	0	0	8	12.3
Coronary Artery Disease	7	4.2	1	4.5	6	9.2
Cerebral Vascular Disease	3	3.4	1	4.5	2	3.1
Congestive Heart Failure	2	1.2	1	4.5	1	1.5
Peripheral Vascular Disease	0	0	0	0	0	0

Note: SD=standard deviation, T2DM=type 2 diabetes mellitus

[†]n=86 for entire cohort, n=22 for prediabetes cohort, n=65 for T2DM cohort

*p<0.05 between prediabetes and T2DM cohorts

The pre-operative means for the laboratory measures of interest including glycemic measures (FPG, A1c), triglycerides, and fasting lipid panel are presented in Table 4.2. Patients in the prediabetes cohort had an average A1c of 5.9 ± 0.3% and FPG of 5.8 ± 0.6 mmol/L. The average A1c and FPG for those in the T2DM cohort were 7.8 ± 1.4% and 8.5 ± 2.9 mmol/L, respectively. Average levels of triglycerides and the average ratios of cholesterol/HDL were higher than the reference range for both cohorts. The prediabetes cohort had statistically significant ($p<0.05$) lower levels of both A1c and FPG compared to the T2DM cohort whereas the T2DM cohort had statistically significant ($p<0.05$) lower levels of total cholesterol and LDL compared to the prediabetes cohort.

Table 4.2

Baseline Laboratory Results of Patients With Prediabetes or T2DM

	Reference Values	**Prediabetes[†] (n=24)**	**T2DM[‡] (n=67)**
Glycemic Measures			
A1c, %	4.0 – 6.0	5.9 ± 0.3*	7.8 ± 1.4
FPG, mmol/L	3.5 – 6.0	5.8 ± 0.6*	8.5 ± 2.9
Triglycerides, mmol/L	0.0 – 1.7	2.1 ± 0.8	2.2 ± 0.8
Fasting Lipid Panel, mmol/L			
Total Cholesterol	2.5 – 6.1	5.2 ± 1.3	4.5 ± 1.1*
HDL	0.7 – 2.0	1.1 ± 0.2	1.0 ± 0.2
LDL	1.4 – 4.2	3.1 ± 1.0	2.6 ± 1.0*
Ratio (Cholesterol/HDL)	0 – 4.0	4.9 ± 1.1	4.8 ± 1.4

Note: Results presented as mean ± standard deviation; A1c=glycated hemoglobin, FPG=fasting plasma glucose, HDL=high density lipoprotein, LDL=low density lipoprotein, T2DM=type 2 diabetes mellitus

[†]Case definition for prediabetes: 6.1 mmol/L ≤ FPG ≤ 6.9 mmol/L, 6.0% ≤ A1c ≤ 6.4%

[‡]Case definition for T2DM: FPG ≥ 7.0 mmol/L, A1c ≥ 6.5%

*$p<0.05$ when compared to the T2DM cohort

4.2 Prediabetes: Results

Of the 24 patients that met the case definition for prediabetes, 3 were lost to follow-up and failed to return for any appointments. Thus, they were not included in the final analysis leaving a sample of 21 patients.

4.2.1 Proportion of Patients Achieving Improvement or Remission. Of the 21 patients with prediabetes that were included in this analysis, 11 (52.4%) completed follow-up at 12 months post-surgery. The remaining patients had not yet reached 12 month follow-up post-surgery. The case definition of normalization was normal glycemic levels for a period of 12 months with the use of pharmacological agents, whereas, the case definition for remission was normal glycemic levels for a period of 12 months without the use of pharmacological agents. Within the first 12 months following surgery 9 (81.8%) patients achieved remission of prediabetes evidenced by normal glycemic measures and no requirement to use antidiabetic medications. The two remaining patients who had not yet achieved remission had normal glycemic measures for a period of 6 months without the use of antidiabetic medications and appeared to be progressing towards achieving remission.

4.2.2 Changes in Glycemic Measures. Prior to surgery and at 3, 6, and 12 months post-surgery, blood samples were collected from patients and the results were forwarded to the research team. The results of the tests with respect to FPG and A1c levels can be found in Figure 4.2. The biggest change in glycemic measures happened within the first three months following surgery with FPG levels decreasing from 5.8 mmol/L to 5.1 mmol/L and A1c decreasing from 5.9% to 5.5%. By six months post-

surgery, the average FPG level had decreased to 5.0 mmol/L and A1c levels remained at 5.5%. These lower levels were maintained up to 12 months post-surgery and were statistically significant ($p<0.05$) at all time points when compared to baseline levels.

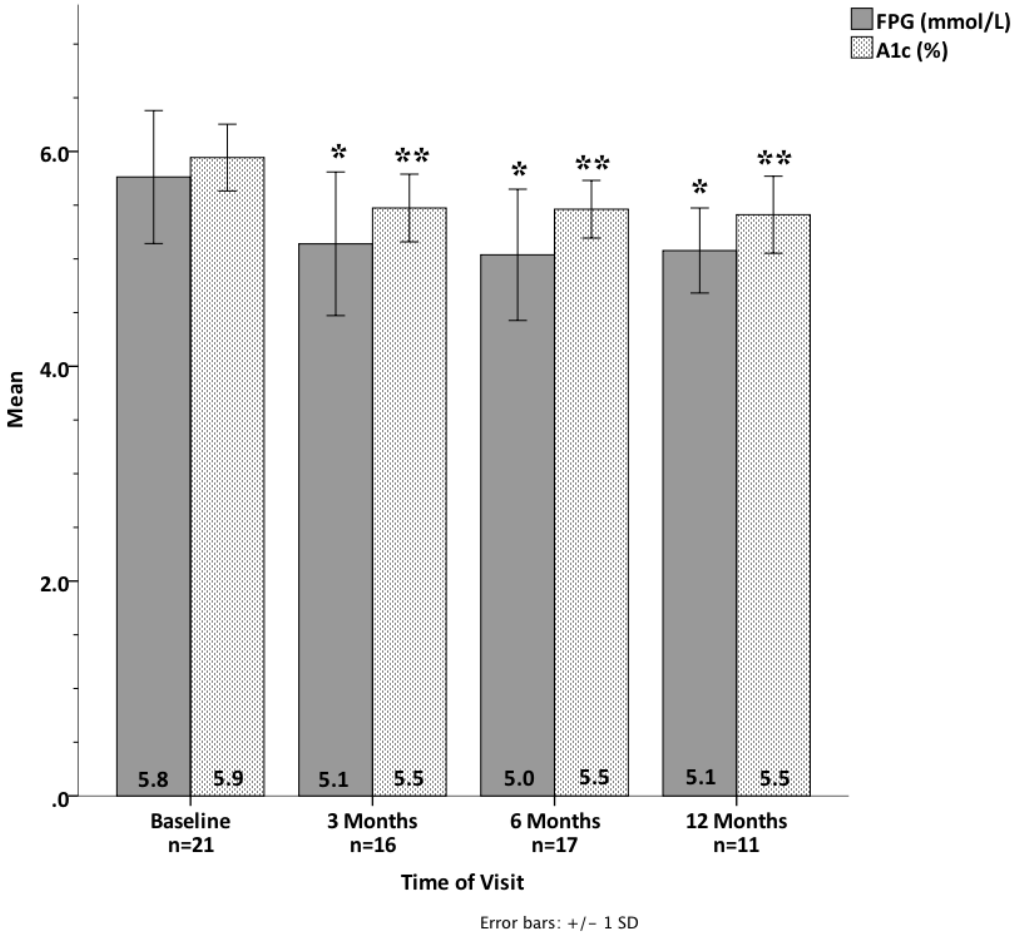

Figure 4.2. **Changes in fasting plasma glucose (FPG, mmol/L) and glycated hemoglobin (A1c, %) in prediabetic patients.** *$p<0.05$ for FPG levels when compared to baseline. **$p<0.01$ for A1c levels when compared to baseline.

4.3 T2DM: Results

Of the 67 patients that met the case definition for T2DM, 8 were lost to follow-up and failed to return for any appointments. Thus they were not included in the final analysis leaving a sample of 59 patients.

4.3.1 Proportion of Patients Achieving Improvement or Remission. Of the 59 patients with T2DM that were included in this analysis, 24 (40.7%) had completed follow-up at 12 months post-surgery. Within the first 12 months following surgery 6 (25%) patients achieved remission of T2DM. Of the 6 patients who achieved remission 4 were considered to be in partial remission, as demonstrated by glycemic measures below the case definition for T2DM without the use of antidiabetic medications for a period of 12 months. The remaining 2 patients were in complete remission with normal glycemic measures without the use of antidiabetic medications for a period of 12 months. Five patients (20.8%) experienced improvement of their diabetes. These patients had glycemic measures below the case definition for diagnosis of T2DM and required either fewer antidiabetic agents or lower doses of those medications to achieve lower glycemic levels. One point of interest is that at 12 months post-surgery, 13 patients (54.2%) had glycemic levels below the diagnostic thresholds identified in the case definition for T2DM and no longer required the use of antidiabetic medications; however, they had not yet maintained these levels for a period of 12 months.

4.3.2 Changes in Glycemic Measures. Figure 4.4 illustrates the changes in A1c and FPG levels post-surgery in patients identified with T2DM. Similar to the prediabetes cohort, the biggest change occurred within the first 3 months following surgery; average FPG levels decreased from 8.6 mmol/L at baseline to 6.4 mmol/L, while average A1c levels decreased from 7.9% to 6.3% during the first 3 months. Glycemic measures continued to decrease after the initial large drop within the first three months following surgery. By 6 months post-surgery, average FPG and A1c levels had decreased to 6.0 mmol/L and 6.2%, respectively. By 12 months post-surgery average FPG levels were 5.6 mmol/L and average A1c levels were 5.9% (n=24). All changes post-surgery were statistically significant ($p<0.05$) when compared to baseline levels.

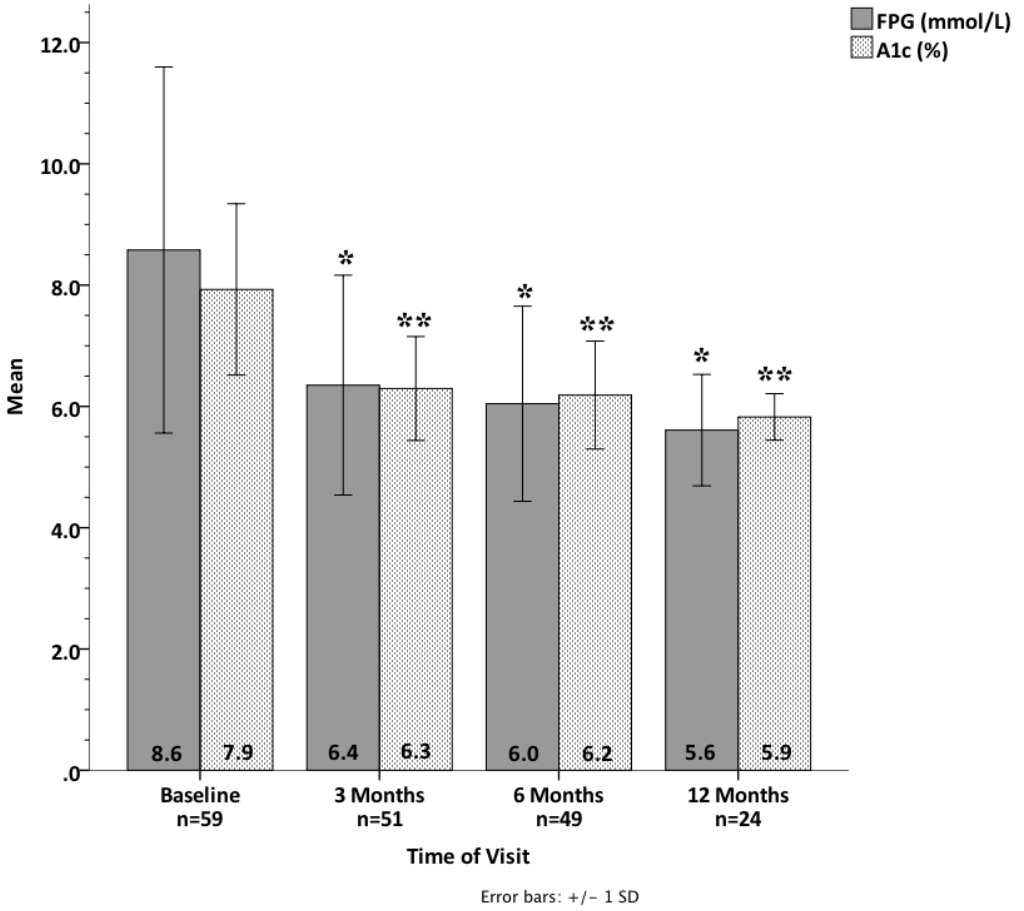

Figure 4.3. **Changes in fasting plasma glucose (FPG, mmol/L) and glycated hemoglobin (A1c, %) in patients with T2DM.** *p<0.05 for FPG levels when compared to baseline. **p<0.01 for A1c levels when compared to baseline.

4.4 Baseline Factors Associated with Remission of Prediabetes and T2DM

A series of chi-square (Fisher's exact test) and Pearson product moment correlation (Pearson's *r*) analyses were performed to determine if any baseline factors were associated with patients achieving remission of prediabetes or T2DM post-surgery. The baseline factors included in the analysis were age, weight, BMI, triglyceride levels, sex, and self-reported medical history of hypertension, dyslipidemia, and/or chronic renal disorder. For patients with T2DM the use of insulin pre-surgery was also analyzed. The continuous variables of age, weight, BMI, and triglyceride levels were analyzed using Pearson's product moment bivariate correlation analysis and the dichotomous variables of sex, self-reported medical history, and insulin use were analyzed using chi-square tests specifically Fisher's exact test. Due to the small sample sizes for the prediabetes (n=11) and T2DM (n=24) cohorts Fisher's Exact Test results were reported when cells in the 2x2 tables had expected counts less than 5. The results of the analyses for the prediabetes and T2DM cohorts are presented in Tables 4.3 and 4.4, respectively.

Within the prediabetes cohort, weight was the only factor associated with remission following LSG. There was a strong, negative correlation between the two variables, r=-0.71, n=11, p=0.01. Within the T2DM cohort none of the included baseline factors were associated with patients achieving remission post-surgery. These results should be interpreted with caution because sample sizes are small, thus the number of patients achieving the outcome is also small, thereby making it difficult to detect associations that may be present.

Table 4.3

Univariate association of selected baseline factors with remission of prediabetes following LSG (n=11)

	Remission (n=9)	**No Remission (n=2)**	**p-value**
Age, years	45.6 ± 9.8	58.5 ± 5.0	0.11
Weight, kg	122.7 ± 15.3	157.0 ± 4.5	0.01
BMI, kg/m^2	45.8 ± 5.5	54.5 ± 8.2	0.09
Triglycerides	1.8 ± 0.6	2.1 ± 0.3	0.61
Sex (Female)	8	1	0.35
Medical History			
Hypertension	7	1	0.38
Dyslipidemia	3	2	0.44

Note: LSG=laparoscopic sleeve gastrectomy. Values are presented as mean ± standard deviation for continuous data or as frequencies for dichotomous variables.

Table 4.4

Univariate association of selected baseline factors with remission of T2DM following LSG (n=24)

	Remission (n=6)	**No Remission (n=18)**	**p-value**
Age, years	44.3 ± 4.5	49.8 ± 10.8	0.24
Weight, kg	131.3 ± 12.6	138.4 ± 24.6	0.51
BMI, kg/m^2	49.4 ± 6.6	50.4 ± 5.7	0.71
Triglycerides, mmol/L	2.3 ± 1.2	2.3 ± 0.8	1.0
Sex (Female)	6	13	0.28
Medical History			
Hypertension	3	15	0.14
Dyslipidemia	4	15	0.27
Chronic Renal Disorder	2	3	0.57
Insulin Use	1	9	0.34

Note: LSG=laparoscopic sleeve gastrectomy, T2DM=type 2 diabetes mellitus. Values are presented as mean ± standard deviation for continuous data or as frequencies for dichotomous variables.

4.5 Association of weight loss with changes in FPG, A1c, triglycerides, HDL, LDL, and total cholesterol and overall remission of prediabetes and T2DM

A series of Pearson's product moment correlation analyses (Pearson's *r*) were carried out to determine if the amount of weight loss 12 months following LSG was associated with changes in blood pressure or levels of FPG, A1c, triglycerides, HDL, LDL, or total cholesterol in prediabetic and diabetic patients. The results of the analyses for the prediabetic and T2DM cohorts are presented in Tables 4.5 and 4.6, respectively. Also, the association between weight loss and remission of prediabetes and T2DM was explored using Pearson's product moment correlation (Pearson's *r*) analyses.

At 12 months post-surgery, the 11 prediabetic patients with complete 12 month data achieved a weight loss of 37.1 ± 11.1 kg. This change in weight was not associated with changes in blood pressure or levels of FPG, A1c, triglycerides, HDL, LDL, or total cholesterol 12 months following LSG. Furthermore, the 12-month weight loss of prediabetic patients was not associated with remission of prediabetes 12 months post-surgery ($p=0.76$).

The 24 T2DM patients with complete 12-month data achieved a weight loss of 36.5 ± 13.4 kg 12 months post-surgery. Two factors, a decrease in FPG (-2.3 ± 2.2 mmol/L, $p<0.01$) and an increase in HDL (0.2 ± 0.2 mmol/L, $p=0.01$) were associated with weight loss 12 months following LSG. There was a strong, negative correlation between the amount of weight lost and change in FPG, $r=-0.59$, $n=22$, $p<0.01$ and a strong, negative correlation between weight loss and change in HDL, $r=-0.51$, $n=23$, $p=0.01$, 12 months post-surgery. However, the amount of weight lost was not associated

with remission of T2DM 12 months after LSG (p=0.39). These results should be interpreted with caution because sample sizes are small, thereby making it difficult to detect associations that may be present.

Table 4.5

Univariate association of changes in blood pressure and selected laboratory values with weight loss 12 months following LSG in prediabetic patients (n=11)

	Change	**p-value**
Blood Pressure, mmHG		
Systolic	-4.8 ± 12.9	0.17
Diastolic	-4.6 ± 15.1	0.36
FPG, mmol/L	-0.55 ± 0.72	0.19
A1c, %	-0.42 ± 0.26	0.67
Triglycerides, mmol/L	-0.68 ± 0.63	0.90
HDL, mmol/L	0.35 ± 0.24	0.27
LDL, mmol/L	-0.23 ± 1.1	0.50
Total Cholesterol, mmol/L	-0.19 ± 1.3	0.69

Note: A1c=glycated haemoglobin, FPG=fasting plasma glucose, HDL=high-density lipoprotein, LDL=low-density lipoprotein, LSG=laparoscopic sleeve gastrectomy. Values are presented as mean ± standard deviation.

Table 4.6

Univariate association of changes in blood pressure and selected laboratory values with weight loss 12 months following LSG in diabetic patients (n=24)

	Change	**p-value**
Blood Pressure, mmHg		
Systolic	-13.2 ± 16.3	0.47
Diastolic	-7.3 ± 11.4	0.80
FPG, mmol/L	-2.3 ± 2.2	<0.01
A1c, %	-1.7 ± 1.2	0.08
Triglycerides, mmol/L	-0.8 ± 0.9	0.15
HDL, mmol/L	0.2 ± 0.2	0.01
LDL, mmol/L	0.3 ± 0.9	0.89
Total Cholesterol, mmol/L	0.2 ± 0.9	0.29

Note: A1c=glycated haemoglobin, FPG=fasting plasma glucose, HDL=high-density lipoprotein, LDL=low-density lipoprotein, LSG=laparoscopic sleeve gastrectomy. Values are presented as mean ± standard deviation.

4.6 Secondary Outcomes: Changes in Weight, Blood Pressure, Triglycerides and Cholesterol, and Changes in Antidiabetic Medication Use

Changes post-surgery in weight loss measures, blood pressure, triglycerides and fasting lipid panel levels for both the prediabetes and T2DM cohorts are outlined in Table 4.7. Within the first 6 months following surgery, patients in the prediabetes and T2DM cohorts had lost an average of 29.8 ± 9.2 kg and 29.1 ± 8.4 kg, respectively. In the prediabetes cohort, average BMI decreased from 46.9 ± 6.8 kg/m^2 to 36.2 ± 5.3 kg/m^2 ($p<0.05$) at 6 months following surgery. Within the first 6 months post-surgery, patients with prediabetes had a %EWL of 45.2 ± 9.4% and had lost an average of 22.9 ± 4.6% of their initial body weight. Similar changes were seen in the cohort of patients with T2DM. In the first 6 months post-surgery, average BMI decreased from 49.6 ± 7.0 kg/m^2 to 39.5 ± 6.0 kg/m^2 ($p<0.05$), %EWL was 39.1 ± 10.0%, and patients had lost on average 20.8 ± 4.6% of their initial body weight. Changes in weight and BMI post-surgery were statistically significant ($p<0.05$) for both cohorts at all follow-up visits compared to baseline. Blood pressure was significantly lower ($p<0.05$) at all follow-up visits compared to baseline in only the T2DM cohort of patients.

Changes in serum levels of triglycerides decreased at each time point post-surgery and these changes were statistically significant ($p<0.05$) for both cohorts. For patients with prediabetes, triglycerides decreased from 1.9 ± 0.6 mmol/L to 1.4 ± 0.5 mmol/L ($p<0.05$) within 6 months and for patients with T2DM, triglyceride levels decreased from 2.1 ± 0.8 mmol/L to 1.4 ± 0.5 mmol/L ($p<0.05$). Levels of HDL remained relatively constant in each cohort, with slight increases at 6 and 12 months, both of which were

statistically significant. Levels of low-density lipoprotein (LDL) were statistically significantly ($p<0.05$) lower at 3 months compared to baseline for the prediabetes cohort; however, for the T2DM cohort LDL at 12 months was statistically significantly ($p<0.05$) lower compared to baseline. For both cohorts, total cholesterol levels showed a statistically significant ($p<0.05$) decrease within 3 months following surgery. Fasting ratios (cholesterol/HDL) were lower at each time point post-surgery and these changes were statistically significant ($p<0.05$) compared to baseline for both cohorts.

Table 4.7

Changes in weight, BMI, blood pressure, triglycerides, and fasting lipid panel in patients with prediabetes and T2DM

	Prediabetes				T2DM			
	Baseline (n=21)	**3 Months (n=18)**	**6 Months (n=18)**	**12 Months (n=17)**	**Baseline (n=59)**	**3 Months (n=53)**	**6 Months (n=54)**	**12 Months (n=24)**
Weight, kg	128.0 ± 22.3	106.8 ± 19.1*	98.7 ± 15.8*	92.1 ± 16.1*	139.3 ± 24.7	117.8 ± 21.4*	110.9 ± 21.1*	99.7 ± 13.5*
Absolute Change in Weight, kg	-	20.7 ±6.0	29.8 ± 9.2	40.2 ± 13.4	-	21.0 ± 5.9	29.1 ± 8.4	37.0 ± 12.8
BMI, kg/m^2	46.9 ± 6.8	39.5 ± 6.1*	36.2 ± 5.3*	33.4 ± 4.7*	49.6 ± 7.0	42.2 ± 6.2*	39.5 ± 6.0*	36.8 ± 4.0*
%EWL	-	32.1 ± 7.7	45.2 ± 9.4	58.1 ± 15.1	-	28.6 ± 7.4	39.1 ± 10.0	48.8 ± 10.1
%AWL	-	16.1 ± 3.3	22.9 ± 4.6	30.2 ± 7.8	-	15.1 ± 3.1	20.8 ± 4.6	26.6 ± 6.2
Blood Pressure, mmHg								
Systolic	131 ± 12	126 ± 13	126 ± 15	129 ± 18	130 ± 14	121 ± 16*	119 ± 12*	123 ± 17*
Diastolic	83 ± 10	81 ± 10	81 ± 9	80 ± 11	80 ± 10	74 ± 11*	74 ± 10*	75 ± 11*
Fasting Lipid Panel, mmol/L	(n=21)	(n=15)	(n=17)	(n=10)	(n=59)	(n=50)	(n=50)	(n=24)
Triglycerides	1.9 ± 0.6	1.4 ± 0.5*	1.4 ± 0.5*	1.3 ± 0.5*	2.1 ± 0.8	1.6 ± 0.5*	1.4 ± 0.5*	1.5 ± 0.5*
HDL	1.1 ± 0.2	1.1 ± 0.1	1.2 ± 0.2*	1.5 ± 0.3*	1.0 ± 0.2	1.0 ± 0.2	1.1 ± 0.2*	1.3 ± 0.3*
LDL	3.1 ± 1.1	2.6 ± 0.8*	2.7 ± 0.8	3.0 ± 1.1	2.6 ± 1.0	2.5 ± 1.0	2.6 ± 1.0	3.0 ± 0.8*
Total Cholesterol	5.0 ± 1.3	4.4 ± 0.9*	4.6 ± 1.0	5.1 ± 1.1	4.5 ± 1.0	4.2 ± 1.1*	4.3 ± 1.0	4.9 ± 0.9
Fasting Ratio (Cholesterol/HDL)	4.8 ± 1.1	4.1 ± 1.0*	3.9 ± 0.9*	3.6 ± 1.1*	4.8 ± 1.3	4.3 ± 1.3*	4.1 ± 1.2*	4.0 ± 1.0*

Note: %AWL=percent absolute weight loss, BMI=body mass index, %EWL=percent excess weight loss, HDL=high-density lipoprotein, LDL=low-density lipoprotein, T2DM=type 2 diabetes mellitus. Analysis was carried out using generalized estimating equations.

*p<0.05 compared to baseline

As previously discussed, serum levels of triglycerides can be indicative of insulin resistance; as T2DM improves and insulin resistance decreases, triglyceride levels should also improve. Figure 4.4 illustrates the changes in BMI and levels of A1c and triglycerides post-surgery. All three variables decreased almost in parallel post-surgery; however, the most dramatic decreases in BMI, A1c, and triglycerides occurred within the first three months following surgery. Average BMI and levels of A1c decreased at each visit post-surgery. There was a slight increase in triglyceride levels at 12 months post-surgery compared to levels at 6 months but this could potentially be due to the low number of patients who had returned at 12 months.

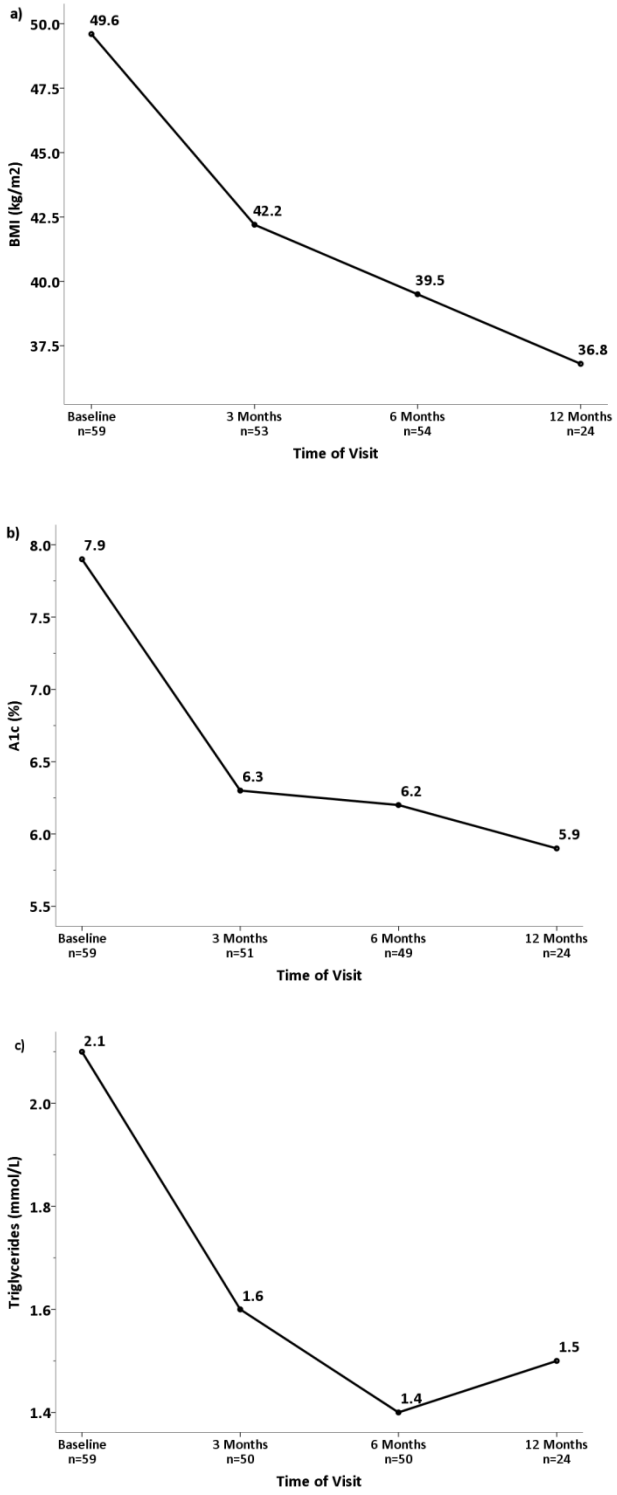

Figure 4.4. **T2DM cohort, changes in: a) BMI (kg/m^2), b) A1c (%), and c) Triglycerides (mmol/L) post-surgery.** A1c=glycated hemoglobin, BMI=body mass index.

In examining the changes in medication use post-surgery the focus was on the T2DM cohort of patients as only one patient in the prediabetes cohort was taking antidiabetic medications prior to surgery and this patient no longer required the use of medication post-surgery. The antidiabetic medications included in this analysis are biguanide (metformin), sulfonylureas (gliclazide, glyburide), alpha glucosidase inhibitor (acarbose), DPP-4-inhibitors (saxagliptin, sitagliptin), meglitinides (repaglinide, nateglinide), thiazolidinediones (pioglitazone, rosiglitazone), GLP-1 receptor agonists (liraglutide), rapid-acting insulin (insulin lispro, insulin aspart), fast-acting insulin (regular insulin), intermediate-acting insulin (insulin NPH), and long-acting insulin (insulin glargine, insulin detemir).

At baseline, 42 patients (71.2% of the sample) with T2DM were taking antidiabetic medications. The 15 (25.4%) patients who were not taking antidiabetic medications at baseline were not prescribed medications for diabetes at any time post-surgery; therefore, the analysis will focus on the 42 patients who were taking antidiabetic medications prior to LSG. The changes in medication use post-surgery are presented in Table 4.8. Within one month after surgery, only 20 of 41 (48.8%) patients who were taking antidiabetic medications before surgery were still taking medication. By the 6 month follow-up, only 16 of 34 (47.1%) patients still required the use of antidiabetic medications. With respect to the number of medications patients required, at baseline the number of medications ranged from 1 to 4 with a mean value of 2.0 ± 1.0 medications but by 6 months post-surgery patients required only 1 or 2 medications with an average of 1.3 ± 0.4. All classes of antidiabetic medications show decreases in the proportion of people

taking medications at each visit post-surgery as well as decreases in the average dose of medication required. Of particular interest is the change in insulin use post-surgery. At baseline, 30 of 42 (71.4%) patients reported using insulin but at 6 months, only 6 of 34 (17.6%) patients still required insulin for diabetes management.

To aid the discussion of changes in HDL, LDL, triglycerides, and total cholesterol, Table 4.9 presents data on changes in the use of HMG CoA Reductase Inhibitors, or statins, post-surgery in the diabetic population. The statins of interest are rosuvastatin, atorvastatin, simvastatin, pravastatin, and lovastatin. At baseline, 31 patients (52.5% of the sample [n=59]) with T2DM were taking statins. By 6 months post-surgery, 18 of 25 (72.0%) patients still required the use of statins. Of the five statins of interest, patients were only ever prescribed rosuvastatin, atorvastatin, or pravastatin. All three statins showed a decrease in use and dose post-surgery; however, by 6 months post-surgery, patients no longer required the use of pravastatin. While the use of statins did decrease post-surgery the reduction was not as substantial as was seen in the use of antidiabetic medications post-surgery.

Table 4.8

Changes in antidiabetic medication use before and after patients with T2DM underwent LSG

	Baseline (n=42)	**1 Month (n=41)**	**3 Months (n=36)**	**6 Months (n=34)**	**12 Months (n=20)**
Taking Antidiabetic Medications, n(%)	**42 (100.0)**	**20 (48.8)**	**16 (44.4)**	**16 (47.1)**	**5 (25.0)**
Average Number of Medications, mean ± SD [Min-Max]	2.0 ± 1.0 [1-4]	1.7 ± 0.8 [1-4]	1.7 ± 0.9 [1-4]	1.3 ± 0.4 [1-2]	1.0 ± 0.0 [1]
Biguanide					
Metformin, n(%)	**34 (81.0)**	**10 (24.4)**	**13 (36.1)**	**13 (38.2)**	**4 (20.0)**
Average Dose (mg)	1619 ± 556 [500-2550]	1472 ± 740 [500-2550]	1254 ± 615 [250-2000]	1163 ± 709 [425-2500]	1231 ± 888 [425-2000]
Sulfonylureas, n(%)	**11 (26.2)**	**4 (9.8)**	**3 (8.3)**	**2 (5.9)**	**0 (0)**
Gliclazide, n(%)	**7 (16.7)**	**3 (7.3)**	**2 (5.5)**	**1 (2.9)**	**0 (0)**
Average Dose (mg)	118.6 ± 71.3 [30-240]	85.0 ± 72.6 [15-160]	87.5 ± 102.5 [15-160]	30.0 ± 0.0	-
Glyburide, n(%)	**4 (9.5)**	**1 (2.4)**	**1 (2.8)**	**1 (2.9)**	**0 (0)**
Average Dose (mg)	12.5 ± 5.0 [10-20]	20.0 ± 0.0	20.0 ± 0.0	10.0 ± 0.0	-
Alpha-Glucosidase Inhibitor, n(%)	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**
DPP-4 Inhibitors, n(%)	**3 (7.1)**	**1 (2.4)**	**1 (2.8)**	**1 (2.9)**	**0 (0)**
Saxagliptin, n(%)	**1 (2.4)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**
Average Dose (mg)	5.0 ± 0.0	-	-	-	-
Sitagliptin, n(%)	**2 (4.8)**	**1 (2.4)**	**1 (2.8)**	**1 (2.9)**	**0 (0)**
Average Dose (mg)	100 ± 0.0	50 ± 0.0	50 ± 0.0	50 ± 0.0	-
Meglitinides, n(%)	**2 (4.8)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**
Repaglinigde, n(%)	**2 (4.8)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**
Average Dose (mg)	2.5 ± 2.1 [1-4]	-	-	-	-
Nateglinide, n(%)	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**
Thiazolidinediones, n(%)	**1 (2.4)**	**1 (2.4)**	**0 (0)**	**0 (0)**	**0 (0)**
Pioglitazone, n(%)	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**
Rosiglitazone, n(%)	**1 (2.4)**	**1 (2.4)**	**0 (0)**	**0 (0)**	**0 (0)**
Average Dose (mg)	4.0 ± 0.0	4.0 ± 0.0	-	-	-
GLP-1 Receptor Agonist, n(%)	**4 (9.5)**	**1 (2.4)**	**0 (0)**	**0 (0)**	**0 (0)**
Liraglutide, n(%)	**4 (9.5)**	**1 (2.4)**	**0 (0)**	**0 (0)**	**0 (0)**
Average Dose (mg)	1.5 ± 0.3 [1.2-1.8]	1.2 ± 0.0	-	-	-

Insulin, n(%)	**30 (71.4)**	**17 (41.5)**	**10 (27.8)**	**6 (17.6)**	**1 (5.0)**
Rapid-acting, n(%)	**9 (21.4)**	**5 (12.2)**	**3 (8.3)**	**2 (5.9)**	**0 (0)**
Insulin lispro, n(%)	**5 (11.9)**	**4 (9.8)**	**2 (5.6)**	**1 (2.9)**	**0 (0)**
Average Dose, (U)	75.0 ± 48.5 [36-135]	27.0 ± 4.2 [24-30]	30.0 ± 0.0	n/a	-
Insulin aspart, n(%)	**4 (9.5)**	**1 (2.4)**	**1 (2.8)**	**1 (2.9)**	**0 (0)**
Average Dose (U)	110.0 ± 45.8 [60-150]	n/a	n/a	n/a	-
Fast-acting, n(%)					
Regular insulin, n(%)	**5 (11.9)**	**2 (4.8)**	**1 (2.8)**	**1 (2.9)**	**0 (0)**
Average Dose, (U)	68.0 ± 40.0 [21-105]	38.0 ± 31.0 [16-60]	15.0 ± 0.0	n/a	-
Intermediate-acting, n(%)					
Insulin NPH, n(%)	**6 (14.3)**	**3 (7.3)**	**1 (2.8)**	**0 (0)**	**0 (0)**
Average Dose, (U)	66.0 ± 28.0 [42-100]	52.0 ± 14.0 [36-60]	60.0 ± 0.0	-	-
Long-acting, n(%)	**10 (23.8)**	**7 (17.1)**	**5 (13.9)**	**3 (8.8)**	**1 (5.0)**
Insulin glargine, n(%)	**5 (11.9)**	**4 (9.8)**	**2 (5.6)**	**2 (5.9)**	**0 (0)**
Average Dose, (U)	88.6 ± 55.1 [28-175]	49.8 ± 22.4 [24-75]	42.0 ± 25.5 [24-60]	43.0 ± 38.2 [16-70]	-
Insulin detemir, n(%)	**5 (11.9)**	**3 (7.3)**	**3 (8.3)**	**1 (2.9)**	**1 (5.0)**
Average Dose, (U)	121.4 ± 29.4 [90-165]	53.3 ± 40.4 [10-90]	53.3 ± 40.4 [10-90]	25.0 ± 0.0	50.0 ± 0.0

Note: LSG=laparoscopic sleeve gastrectomy, max=maximum, mg=miligrams, min=minimum, n/a=not available, SD=standard deviation, T2DM=type 2 diabetes mellitus, U=units. Average doses reported as mean ± SD and [minimum dose-maximum dose].

Table 4.9

Changes in statin use before and after patients with T2DM underwent LSG

	Baseline (n=31)	**1 Month (n=31)**	**3 Months (n=28)**	**6 Months (n=25)**	**12 Months (n=13)**
Taking Statins, n(%)	**31 (100.0)**	**27 (87.1)**	**23 (82.1)**	**18 (72.0)**	**8 (61.5)**
Rosuvastatin, n(%)	**21 (67.7)**	**19 (70.4)**	**15 (65.2)**	**14 (77.8)**	**5 (62.5)**
Average Dose (mg)	13.3 ± 5.8 [5-20]	13.0 ± 6.2 [5-20]	12.3 ± 6.2 [5-20]	11.4 ± 6.0 [5-20]	13.0 ± 6.7 [5-20]
Atorvastatin, n(%)	**9 (29.0)**	**7 (25.9)**	**7 (30.4)**	**4 (12.9)**	**3 (37.5)**
Average Dose (mg)	22.5 ± 18.3 [10-60]	21.4 ± 20.4 [10-60]	22.9 ± 19.8 [10-60]	20.0 ± 14.1 [10-40]	13.3 ± 5.8 [10-20]
Simvastatin, n(%)	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**
Average Dose (mg)	-	-	-	-	-
Pravastatin, n(%)	**1 (3.2)**	**1 (3.7)**	**1 (4.3)**	**0 (0)**	**0 (0)**
Average Dose (mg)	20 ± 0.0	20 ± 0.0	20 ± 0.0	-	-
Lovastatin, n(%)	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**
Average Dose (mg)	-	-	-	-	-

Note: Average doses reported as mean ± SD and [minimum dose-maximum dose]. LSG=laparoscopic sleeve gastrectomy, mg=miligrams, SD=standard deviation, T2DM=type 2 diabetes mellitus.

Chapter 5: Discussion

The current study examined the improvement and remission of prediabetes and T2DM following LSG in patients living in NL by reporting the proportion of patients experiencing either improvement or remission at 12 months post-surgery. This study also examined changes in glycemic measures (A1c and FPG), antidiabetic medication use, weight, blood pressure, triglycerides, and fasting lipid panel and explored potential factors associated with remission of prediabetes and T2DM.

The discussion of the results is organized based on the research questions outlined in Chapter 1. The first section describes how this sample of patients compares to other samples with respect to baseline demographics and obesity-related comorbidities. The second section discusses the proportion of patients who achieve improvement or remission of prediabetes as well as changes in glycemic measures for this group. The third section discusses similar outcomes for the T2DM cohort. The fourth section discusses baseline factors that may be associated with the likelihood of a patient achieving remission of prediabetes or T2DM post-surgery. The fifth section assesses the secondary outcomes – changes in weight, blood pressure, triglycerides, fasting lipid panel, and antidiabetic medication use.

5.1 Baseline Demographics, Comorbidity Profile, & Laboratory Values

The demographics and initial levels of FPG and A1c of patients with T2DM undergoing LSG in NL were comparable to other populations that have been studied. The current study reported on a predominantly female diabetic population (76.1%) with an

average age of 45.0 ± 10.4 years and an initial average BMI of 49.3 ± 7.0 kg/m^2. Average pre-operative FPG levels were 8.5 ± 2.9 mmol/L and average levels of A1c were 7.8 ± 1.4% initially. A systematic review by Gill et al. (2010) included 673 patients in 27 studies and reported an average age of 46.6 years that was, on average, 66% female with an average initial BMI of 47.4 kg/m^2. Initial levels of FPG were, on average, 10.1 mmol/L and average initial A1c values were 7.9% (Gill et al., 2010). While the average FPG levels in the systematic review were slightly elevated when compared to this study, the populations appear to be similar in all other aspects related to baseline characteristics.

A study by Padwal et al. (2012) described the characteristics of the population receiving publicly funded bariatric surgery in Canada. The sample (n=91) in the current study showed similarities to the Canadian population undergoing bariatric surgery with respect to average age, ethnicity, proportion of females, and level of education. For example, in Canada, the average age of surgical patients is 43.6 ± 11.1 years, 87.1% are Caucasian, and 82% of the population is female. In the current study, the average age was 45.6 ± 10.4 years, 90.1% of the sample was Caucasian, and 76.9% of the sample was female. The authors described patients undergoing surgery as highly educated, with 56.9% of the eligible population having received some post-secondary education, similar to that of the current study sample (63.9% of the sample had received a college diploma or university degree). However, the prevalence of obesity-related comorbidities was much higher in the NL sample compared to the Canadian population undergoing bariatric surgery. Of the Canadian population receiving surgery, 13.1% reported a history of hypertension compared to 67.8% of the current sample, 21.1% report a history of diabetes

compared to 62.8%, 10.9% report a history of sleep apnea compared to 61.6%, and only 2.4% report a history of dyslipidemia compared to 60.5% of the current sample. This could be a consequence of candidate pre-selection in other health care jurisdictions in Canada, whereby healthier patients are selected to undergo bariatric surgery in an effort to not impact surgical risk or length of stay.

5.2 Prediabetes

There is very little published data on the effects of LSG on patients with obesity and prediabetes. Only one published study was identified on this topic; however, the definitions of improvement and remission were different from those used in the current study as was the diagnostic technique used for identifying patients with prediabetes (Natoudi et al., 2014).

5.2.1 Proportion of Patients Achieving Improvement or Remission of Prediabetes.

In the current study sample, 11 patients (52.4%) had complete 12 month data and were therefore included in this analysis. The study by Natoudi et al. (2014) reported outcomes for 20 patients with prediabetes; however, the sample was only 25% female compared to the 79.2% female sample of prediabetic patients in the current study.

Within 12 months post-surgery, Natoudi et al. (2014) reported that all 20 patients who were initially classified as prediabetic were reclassified as having normal glycemic measures. The current study reported that 9 patients, or 81.8% of the sample with prediabetes that had complete 12 month data, had achieved remission of prediabetes and the remaining 2 patients had normal glycemic measures for a period of 6 months. The

results from this analysis are similar to those obtained by Natoudi and colleagues (2014) however, more follow-up is needed on this specific patient population before any conclusions can be drawn on the effect of LSG on prediabetes.

5.2.2 Changes in Glycemic Measures. The current study suggests that patients with prediabetes achieved significant changes in FPG and A1c levels within 12 months post-surgery. The study by Natoudi et al. (2014) reported only on changes in oral glucose tolerance test results thus direct changes in glycemic measures cannot be compared. The largest change in glycemic measures in the current study happened within the first 3 months following surgery with FPG decreasing from 5.8 mmol/L to 5.1 mmol/L ($p<0.01$) and A1c levels decreasing from 5.9% to 5.5% ($p<0.01$). Normal levels for FPG and A1c are considered to be 6.0 mmol/L and 6.0%, respectively and by 3 months post-surgery the patients within one standard deviation of the average value had achieved normal levels of FPG and A1c. At both 6 and 12 months following surgery FPG and A1c levels remained consistent with the 3 month results, although the findings should be interpreted with caution as only 11 patients (52.4%) had returned for the 12 month visit at the time of this analysis. The mechanism behind the immediate decline in levels of FPG and A1c within the first 3 months following LSG in this study is not certain. It may be attributed to weight loss but it is more likely attributed to either changes in the secretion of gut hormones or reduced caloric intake post-surgery. These mechanisms will be discussed further in section 5.3.2.

5.3 T2DM

5.3.1 Proportion of Patients Achieving Improvement or Remission of T2DM.

24 T2DM patients (40.7%) had complete 12 month data and were therefore included in this analysis. This sample size is similar to that of other studies looking at the effectiveness of LSG on the improvement or remission of T2DM in a 12 month period as outlined in the literature review which had a median sample size of 22 patients (range: 6-75) (Desiderio et al., 2013a, Gill et al., 2010, Slater et al., 2011).

Of the 11 studies in the literature review that reported results on improvement of T2DM after a period of 12 months, a range of 2%-86% of patients achieved improvement with a median value of 24% (Desiderio et al., 2013a, Gill et al., 2010, Slater et al., 2011). The proportion of patients that experienced *improvement* of T2DM in the current study was 20.8% which is on the lower end of the spectrum compared to other published studies. A total of 14 studies reported on *remission* of T2DM 12 months post-surgery with a range of 14%-98% achieving remission (median 71%) compared to 25% of the current sample achieving remission within 12 months (Desiderio et al., 2013a, Gill et al., 2010, Slater et al., 2011). While the proportions of patients achieving improvement and remission in the current study are lower than those reported in the literature, not all studies are using the same definition of improvement and remission as no standard definition has been accepted; thus, it is hard to make comparisons between studies.

Two recent studies with a follow-up period of 12 months have used the same criteria for improvement and remission as the current study. A study conducted by Slater et al. (2011) comprised of 22 patients reported 75% of patients achieved remission and

25% experienced improvement of T2DM. A second study by Desiderio et al. (2013a) reported on the 12 month outcomes of 15 patients noting 40% of patients achieved complete remission and 33.3% achieved partial remission of T2DM while the remaining 26.7% were stable in their disease status. When comparing the current results to studies with similar definitions of improvement and remission, the current data suggests lower rates of remission and improvement within the first 12 months following surgery. The reason for these discrepancies is not clear, but it may lie in the pre-operative differences between the two samples. The sample of patients in the study by Slater et al. (2011) was predominantly male (79% versus 23.9%) and was older (55.3 years versus 45 years); however, Slater and colleagues described a sample in which 55% of patients were using injectable insulin whereas 71.4% of patients in the current study were using injectable insulin at baseline. This could indicate that patients in the current study had more advanced diabetes and would therefore be less likely to experience remission of T2DM within the first 12 months following surgery. The study by Desiderio et al. (2013a) also described an older population (58.8 years versus 45 years) but with a lower average pre-operative BMI than that of the current study (37.9 ± 1.5 kg/m^2 versus 49.3 ± 7.0 kg/m^2). The discrepancy in BMI could be the reason why Desiderio and colleagues reported a higher rate of remission than the current study as obesity is a major risk factor for the development of T2DM and patients that are more obese may have more severe diabetes or may have been diabetic for a longer period of time, making it less likely for them to achieve remission within just 12 months following surgery.

In contrast, a study by Pournaras et al. (2012) applied the definition of remission recommended by Buse and colleagues (2009) in a retrospective study of diabetic patients undergoing bariatric surgery and reported a remission rate of T2DM of 26% following LSG. The remission rate when the new definition of remission was applied was substantially lower than rates reported in previous studies but was more similar to the 25% rate of remission in the current study. The two samples were similar in most pre-operative characteristics. The sample in the study by Pournaras and colleagues was older (53 years versus 45 years) but had a similar initial average BMI (50 ± 8.0 kg/m^2 versus 49.3 ± 7.0 kg/m^2), FPG (8.9 ± 4.2 mmol/L versus 8.5 ± 2.9 mmol/L), and A1c (7.5 ± 1.5% versus 7.8 ± 1.4%); however, only 32% of patients in the study by Pournaras and colleagues were using insulin before surgery compared to 71.4% of patients in the current study. Thus, it is hard to conclude exactly why the proportions of patients experiencing remission of T2DM in these studies were so similar.

In summary, within the first 12 months post-surgery, improvement or remission of T2DM was seen in 20.8% and 25% of the sample, respectively; however, in this current study, a number of patients had yet to reach their 12-month post-operative appointment, which could affect the estimated percentages of improvement and remission. Due to the stringent case definitions of improvement and remission recommended by Buse et al. (2009), rates of remission of T2DM may be lower in studies using these criteria (Pournaras et al., 2012).

5.3.2 Changes in Glycemic Measures. The current study indicated that patients experienced significant changes in FPG and A1c levels within 12 months post-surgery.

However, considering that only 40.7% of patients had returned at 12 months at the time of analysis, the focus will be on the 6 month results, for which 83.1% of patients had data. Within the first 6 months of having surgery FPG levels decreased on average by 2.6 mmol/L and A1c levels decreased by an average of 1.7%.

Two studies included in the systematic review conducted by Gill et al. (2010) published results on patients just 6 months after surgery and found levels of FPG to decrease by 2.0 mmol/L and 1.7 mmol/L and levels of A1c decreased by 1.6% and 0.5% (Gill et al., 2010). An additional study, which reported only on changes in A1c, observed a decrease of 1.3% within 6 months following surgery (Gill et al., 2010). Compared to these results, the sample in this study exhibited larger changes in both FPG and A1c within just 6 months post-surgery. Interestingly, the largest change in the current study occurred just 3 months after surgery; FPG levels decreased by 2.2 mmol/L to a level of 6.4 ± 1.8 mmol/L and A1c levels decreased by 1.6% to a level of 6.3 ± 0.8% resulting in both average FPG and A1c levels below the diagnostic thresholds identified in the case definition of T2DM. Other published studies have similar findings, with levels of FPG and A1c dropping rapidly in the initial period following surgery (i.e., within the first 3 months) with the rate of change slowing down by 6 months post-surgery (Desiderio et al., 2013a). The study by Desiderio et al. (2013a) reported a pre-surgery FPG level of 9.9 ± 1.7 mmol/L which decreased to 6.3 ± 1.0 mmol/L in just 60 days and remained at this level at both 6 and 12 months post-surgery. Similarly, pre-operative A1c levels were 8.1 ± 0.6 % and these levels dropped down to 6.1 ± 0.6% within the first 60 days following surgery and at 6 months decreased slightly to 5.9 ± 0.6% (Desiderio et al., 2013a).

The reasons for such a rapid change in glycemic measures in the current study and other published literature almost immediately after surgery are still under debate. The glucose-lowering effects of certain bariatric surgical procedures within just days after surgery, before significant weight-loss has occurred, have been known for decades; thus, the predominant hypotheses for these metabolic advantages after bariatric surgery include changed release of GI hormones and surgically induced restriction of food intake (Knop & Taylor, 2013). The change in the delivery of nutrients to the small intestine (i.e., food being delivered to the small intestine faster or to a more distal region of the small intestine) increases the GLP-1 response to a meal thus enhancing the insulin response and lowering blood glucose levels (Knop & Taylor, 2013). It remains to be seen what proportion of the enhanced postprandial insulin secretion is dependent on changes in incretin secretion and also what change in long-term β-cell function results from surgically induced increases in GLP-1 secretion (Knop & Taylor, 2013). With respect to surgically induced restriction of food intake, sudden negative calorie balance induced by any means in diabetic patients will normalize plasma glucose levels within days and this is believed to be the predominant mechanism underlying the early metabolic changes after bariatric surgery (Knop & Taylor, 2013).

In summary, significant changes in glycemic measures occurred as early as 3 months post-surgery. Average decreases in FPG and A1c observed in the current study within 6 months post-surgery were greater than what has been reported in similar studies.

5.4 Factors Associated with Remission of Prediabetes and T2DM

The current study was unable to identify any baseline factors associated with the remission of T2DM following LSG. In contrast, one factor, baseline weight, was associated with remission of prediabetes 12 months post-surgery. This finding could be attributed to the fact that obesity is associated with insulin resistance; patients with lower weights and thus, less insulin resistance, may not have developed as severely elevated glucose levels prior to surgery making it more likely for them to experience remission due to the metabolic changes following LSG. The small sample size in this analysis could explain why more associations, particularly in the T2DM cohort, were not found. Furthermore, a variable indicative of remission of T2DM (duration of T2DM prior to surgery) was not available in the current study.

Key pre-operative factors identified in the research literature as being predictive of remission of T2DM following bariatric surgery include: duration of T2DM, baseline BMI, baseline FPG and A1c levels, insulin use, waist circumference, and C-peptide levels (Casella et al., 2011; Lee et al., 2012; Robert et al., 2013). These studies have larger sample sizes (e.g., at least double the number of participants of the current study) and remission rates greater than 50%, thus making them better able to determine pre-operative indicators of remission.

Furthermore, weight loss 12 months post-surgery was not associated with any changes in secondary outcomes following surgery for the prediabetic cohort; however, in the T2DM cohort, weight loss was associated with decreases in FPG ($p<0.01$) and increases in HDL ($p=0.01$) 12 months post-surgery. While weight loss alone cannot

entirely explain the improvement of T2DM post-surgery, the underlying factors contributing to weight loss may play a role in amelioration of FPG and HDL post-surgery. One of the factors shown to contribute to weight loss is an increase in GLP-1 production post-surgery which inhibits the release of glucagon and acts on the pancreas to secrete insulin (Miras & le Roux, 2013), both of which would ultimately lower levels of FPG. This increase in GLP-1 has also been hypothesized as a factor that may help explain the increase in HDL post-surgery (Zhang et al., 2011).

5.5 Secondary Outcomes: Changes in Weight, Blood Pressure, Triglycerides, Cholesterol, and Antidiabetic Medication Use

Both the prediabetes and T2DM cohorts in the current study experienced significant changes in weight loss measures following LSG. A Canadian study by Behrens et al. (2011) that followed patients for an average of 10 months (range: 2-23 months) reported that patients had an average weight loss of 27.4 kg with an average decrease in BMI of 10.4 kg/m^2. These figures are comparable to those in the current study which reported an average weight loss of 29.3 kg and 28.4 kg for the prediabetes and T2DM cohorts, respectively, followed by an average decrease in BMI of 10.7 kg/m^2 for the prediabetes cohort and 10.1 kg/m^2 for the T2DM cohort within 6 months following surgery. Within 6 to 36 months following LSG, %EWL is expected to range from 45% to 60% (Victorzon, 2012), comparable to the results seen in the current study with patients with prediabetes having lost 45.2 ± 9.4% of their excess weight and patients with T2DM having lost 39.1 ± 10.0% of their excess weight 6 months post-surgery.

Bariatric surgical procedures were designed to restrict food intake and cause nutrient malabsorption; however, evidence suggests that these factors make minimal contributions to weight loss (Miras & le Roux, 2013). Instead, weight loss induced by bariatric surgery is a result of decreased hunger, increased satiation during a meal, changing food preferences, and energy expenditure (Miras & le Roux, 2013). Following LSG, postprandial levels of PYY and GLP-1 are markedly higher than before surgery (Miras & le Roux, 2013). PYY and GLP-1 are released in response to a meal and act on the hypothalamus to decrease food intake; however, it is still uncertain if GLP-1 is necessary for LSG-induced weight loss (Miras & le Roux, 2013). In contrast, levels of ghrelin, a hunger-inducing hormone that increases food intake, are reduced following LSG (Miras & le Roux, 2013). Changes in these three hormones following LSG act to decrease hunger and increase satiation during a meal ultimately resulting in restricted food intake by patients (Miras & le Roux, 2013).

Bariatric surgical procedures also have an effect on the types of macronutrients chosen by patients, though most of the research has been conducted in patients that have undergone RYGB (Miras & le Roux, 2013). Regardless of dietary advice received by patients pre- or post-surgery, following RYGB, patients prefer to eat food low in fat and/or sugar suggesting that food preferences are predominantly affected by physiological processes as opposed to dietary recommendations and social acceptability bias (Miras & le Roux, 2013). While some animal studies have shown that LSG is associated with similar changes in food preference as is seen following RYGB, more research is needed to truly understand changing food preferences following LSG (Miras & le Roux, 2013).

In looking at changes in energy expenditure following LSG, rodent models have demonstrated either stability or a decrease in resting energy expenditure post-surgery (Miras & le Roux, 2013). However, human and animal studies have demonstrated an increase in diet-induced energy expenditure following RYGB but the underlying mechanisms are still unknown (Miras & le Roux, 2013). More research is needed to assess the effects of LSG on diet-induced energy expenditure.

Changes in blood pressure post-surgery for the prediabetes cohort were not significant when compared to baseline but did decrease from an average of 131/83 ± 12/10 mmHg to 126/81 ± 15/9 mmHg within 6 months post-surgery. By 12 months post-surgery with 17 patients (81.0%) having returned for follow-up the average blood pressure was 129/80 ± 18/11 mmHg. Changes in blood pressure for patients with T2DM did prove to be statistically significant at each follow-up appointment post-surgery compared to baseline. Initially in this cohort the average blood pressure was 130/80 ± 14/10 mmHg which decreased to an average of 119/74 ± 12/10 mmHg within the first 6 months following surgery ($p<0.05$). Existing literature has also reported similar improvements in blood pressure in diabetic populations following LSG. A study by Lee et al. (2011) which did not report on baseline values reported a decrease in both systolic and diastolic blood pressure at 12 months post-surgery to an average level of 124/75 ± 10/9 mmHg which is a similar value to the 12 month blood pressure reported in this study (123/75 ± 17/11) with only 42.4% of the sample having returned at the time of analysis. A study by Desiderio et al. (2013b) investigating the effects of LSG in patients with severe obesity and metabolic disorders also reported significant changes in blood pressure post-

surgery. The baseline average blood pressure was reported as 136/87 ± 19/8 mmHg and decreased to 120/80 ± 13/5 mmHg and 117/78 ± 9/4 mmHg at 6 and 12 months post-surgery, respectively (Desiderio et al., 2013b).

Levels of serum triglycerides decreased significantly in both cohorts in the current study, which is a secondary indicator of improvement in insulin resistance and thus an indicator of improvement of diabetes as well. Initially both cohorts had average triglyceride levels outside the reference range (0.0-1.7 mmol/L). Initial triglyceride levels were 1.9 ± 0.6 mmol/ L and 2.1 ± 0.8 for the prediabetes and T2DM cohorts, respectively. 6 months post-surgery these average levels fell to within the reference range; average triglycerides levels were 1.4 ± 0.5 mmol/L for both cohorts ($p<0.05$). This trend has also been seen in similar studies which have reported triglyceride levels initially higher than the reference range dropping after surgery to levels within the normal reference range (Chowbey et al., 2010; Perathoner et al., 2013).

With respect to serum cholesterol levels, levels of HDL slowly increased post-surgery with both cohorts exhibiting an increase beginning at the 6-month follow-up appointment, which was statistically significant. Both cohorts showed an average increase of 0.1 mmol/L in HDL at 6 months and the 12 month data thus far showed a further increase; however, 12 month results should be interpreted with caution as not all patients had returned for 12 month follow-up at the time of this analysis. This is consistent with the results in a study by Perathoner et al. (2013), which showed an increase in HDL levels of 0.2 mmol/L after an average follow-up time of 17.4 months. As noted in Chapter 4, pre-surgery levels of LDL and total cholesterol were lower in the T2DM cohort than in

the prediabetes cohort. While this is counterintuitive as dyslipidemia is a comorbidity associated with both obesity and T2DM it is likely due to the fact that more diabetic patients were taking statins at baseline (52.5%) than were prediabetic patients (28.6%). A closer examination of levels of LDL and total cholesterol, indicated that both appeared to be decreasing at 3 months following surgery but at both 6 and 12 months follow-up the levels were once again rising and even surpassed the pre-operative means but was only statistically significant for the T2DM cohort. Perathoner and colleagues (2013) reported similar results with respect to total cholesterol with baseline and post-operative levels being equal; however, the authors reported an overall decrease in levels of LDL, although the finding was not statistically significant. Furthermore, the use of statins, which act to decrease levels of triglycerides, LDL, and total cholesterol and increase levels of HDL, decreased slightly following surgery thus medication use was not likely responsible for the changes in lipid profiles post-surgery.

Bariatric surgical procedures can improve dyslipidemia associated with obesity; however, the impact varies based on surgical procedure (Zhang et al., 2011). Malabsorptive procedures have been shown to improve all of the variables in the lipid profile while restrictive procedures like LSG primarily increase HDL, reduce triglycerides, and show modest improvements in total cholesterol (Zhang et al., 2011). The exact mechanism behind these changes in lipid profiles is not clear but increases in ghrelin and GLP-1 production may help explain the effect of LSG on HDL and triglycerides (Zhang et al., 2011). It has also been speculated that the decreased

availability of free fatty acids and the negative energy balance produced by surgery may also contribute to changes in lipid profiles following LSG (Zhang et al., 2011).

Changes in the use of antidiabetic medications post-surgery were analyzed only for patients with T2DM as only one patient with prediabetes was prescribed an antidiabetic agent prior to surgery. The proportion of patients taking antidiabetic agents decreased to 47.1% within 6 months of undergoing LSG. At the 12 month follow-up appointment the number of patients taking antidiabetic medications had decreased to 25% but this should be interpreted with caution as only 20 of 42 (47.6%) patients had returned at the time of analysis. As the proportion of patients taking medications post-surgery decreased, so did the average number of medications that patients required. On average, patients were taking 2.0 ± 1.0 (range: 1-4) medications before surgery and this number decreased to 1.3 ± 0.4 (range: 1-2) at 6 months post-surgery. Within this initial 6 month period after surgery patients who still required the use of antidiabetic agents only required approximately half of the amount of medications they had been initially prescribed. It follows that the proportion of patients taking the major classes of antidiabetic medications also decreased post-surgery. Prior to surgery 81% of patients were taking biguanides, 26.2% were taking sulfonylureas, 7.1% were taking DPP-4 inhibitors, 4.8% were taking meglitinides, 2.4% were taking thiazolidinediones, 9.5% were taking a GLP-1 receptor agonist, and 71.4% were taking insulin with these proportions decreasing to 38.2%, 5.9%, 2.9%, 0%, 0%, 0%, and 17.6%, respectively, 6 months post-surgery. Within 6 months post-surgery patients no longer required the use of drugs from the classes of meglitinides, thiazolidinediones, and GLP-1 receptor agonists.

The results presented in this study are similar to results from other comparable studies. A study by Schauer et al. (2012) showed similar reductions in the proportions of patients requiring the use of biguanides and insulin following LSG. The proportion of patients taking biguanides decreased from 84% to 39% and the proportion of patients taking insulin decreased from 45% to 8% within 12 months post-surgery. Also, similar to the current study, patients were taking a maximum of only 2 antidiabetic agents 12 months following surgery. Another study examining the proportion of patients requiring antidiabetic medications after undergoing LSG found that within 12 months following surgery only 17.7% of patients required the use of antidiabetic agents post-surgery (Ruiz de Gorejuela et al., 2011). Finally, Rosenthal et al. (2009) reported that following LSG oral hypoglycemic agent use decreased from 73% to 30% and insulin use decreased from 27% to 7% 6 months after surgery.

Antidiabetic medications help control blood glucose levels but they often are unable to prevent the progression of diabetes which leads to other macrovascular complications. As patients experience metabolic improvements following LSG and go on to experience either remission or improvement of prediabetes or T2DM their bodies become better able to control blood glucose levels on their own; thus, patients require fewer medications and lower doses of medications, if they require the use of medication at all. The results of the current study indicate that patients require significantly fewer medications within 6 months post-surgery and these results are consistent with what other studies are reporting at 6 months post-surgery in obese, diabetic populations undergoing LSG.

In summary, both the prediabetes and T2DM cohorts achieved weight loss following LSG that was both statistically and clinically significant and as patients experienced improvement or remission of prediabetes or T2DM, triglyceride levels also improved further indicating an improvement in insulin resistance in the sample. Changes in fasting lipid panels were variable, while levels of HDL slowly increased after surgery, levels of LDL and total cholesterol initially decreased but then began to return to, or exceed, pre-operative levels. While all patients experienced lower blood pressure levels post-surgery, only patients in the T2DM cohort experienced changes that were statistically significant. Patients also required fewer antidiabetic medications post-surgery, and a decrease was also seen in the dose of required medications within 12 months post-surgery.

Chapter 6: Strengths and Limitations, Clinical Implications and Knowledge Translation, Future Research, and Conclusions

This chapter will summarize the strengths and limitations, clinical implications and knowledge translation, future research, and conclusions of this study. The first section includes a description and discussion of the strengths and limitations of this study. The second section outlines the clinical implications of this research and the importance of integrated knowledge translation. The third section describes proposals for future research on this topic and the final section summarizes the conclusions of this study.

6.1 Strengths and Limitations

This study had both strengths and limitations a number of which are inherent in its design. The current study was strengthened by multiple factors. This study was a part of the ongoing NL BaSco Study enabling this research to include all patients who had undergone LSG and had consented to take part in research from the time bariatric surgery began being offered in NL in May 2011. Creating a case definition for prediabetes and T2DM eliminated the necessity of relying on self-reported medical history to identify patients with hypergylcemia thus ensuring that the study captured all eligible patients. Also, this research was one of the first studies in a Canadian health care setting to take into consideration what happens to patients with prediabetes following LSG. Other research suggests that by studying this patient population there is a chance to reduce the incidence of T2DM in obese populations through bariatric surgery (Natoudi et al., 2013).

This study had a number of limitations. Selection, sampling, and referral bias are all inherent in inception cohort studies. *Selection bias* in this study exists in the fact that

patients are seeking bariatric surgery on their own, through their family physician, making the sample of patients not truly random. The sample population seeking bariatric surgery may be more motivated to lose weight and make the necessary lifestyle changes to improve their health; thus, the outcomes seen in this sample may be overestimated compared to the general population which leads to the second type of bias, sampling bias.

Sampling bias is error that arises due to the sample selection. Once patients have consented to be part of the study and provide data on their health outcomes to the research team the actual collection of data is dependent on patients returning for follow-up appointments. When patients do not return for appointments, no data is collected and the research team cannot make any conclusions about their health outcomes post-surgery. The group of patients that do return post-surgery are adhering to follow-up and are most likely to be patients having a positive post-surgery experience thus potentially skewing the results in a more positive way.

Referral bias occurred in the method used to identify patients with either prediabetes or T2DM pre-operatively. While creating a case definition for prediabetes and T2DM was helpful in capturing patients who did not self-report a medical history of diabetes, it cannot be considered as a diagnosis of either condition as the gold standard test was not used. The gold standard for diagnosing diabetes would involve an OGTT which is not required before undergoing bariatric surgery; thus, a case definition using FPG and A1c levels was created based on recommendations by the CDA.

However, the results of the study are generalizable to other bariatric surgery populations with compliant patients. The average age of the current sample was 45.6 ± 10.4 years, 90.1% were Caucasian, 76.9% of the sample was female, and average pre-surgery BMI was 48.6 ± 7.1 kg/m^2. The cohort characteristics were similar to bariatric surgical patients across the country (Padwal et al., 2012), increasing the generalizability of the study results to other Canadian jurisdictions as well as other publicly funded health care systems.

As previously mentioned, baseline levels of FPG, triglycerides, LDL, and total cholesterol and baseline weight and blood pressure were recorded after patients had completed a one week full fluid diet, possibly resulting in an underestimation of these baseline values as they would be lower following the diet. Of all of the baseline levels mentioned above, FPG could most certainly be significantly reduced within one week of a full fluid diet; it is likely to be the one factor most affected within this time frame. The results of the current study should be interpreted with caution because, if these values had been recorded prior to the full fluid diet, then the magnitude of changes in blood glucose levels, weight, blood pressure, etc. would be even greater than what was reported. Furthermore, the prevalence of blood glucose levels diagnostic of prediabetes and T2DM could also be higher prior to the full fluid diet than after its initiation; thus, leading to an underestimation of the prevalence of these conditions in the current cohort of patients. This may also lead to information bias.

Information bias, specifically *misclassification bias,* is another type of bias that may be present in this study. This type of bias may have occurred as there is a chance that

diseased patients (i.e., patients with prediabetes or T2DM) may have been classified as non-diseased and vice versa for the reason stated above or also because the identification of disease state was not carried out by a medical professional who was familiar with each patient's medical history.

Finally, this study reports short-term results within 12 months following surgery and is an analysis of a subsample of the population of the NL BaSco Study. For a patient to be considered as having improved prediabetes or T2DM or in remission of either disease the criteria must have been met for a period of 12 months; thus, this study is only capturing patients who experience improvements immediately following surgery (i.e., normal glycemic measures 3 months post-surgery). This may have caused the estimate of the proportion of patients experiencing remission post-surgery to be lower than what is expected based on other research. Also, by only reporting on 12 month data there is no indication about the duration of improvement or remission of prediabetes or T2DM following LSG. While the results of this analysis are promising, the small sample size limits the ability to make any definitive statements on the effectiveness of LSG on the improvement or remission of T2DM. While extensive literature exists on this topic there is limited evidence available on predictors of remission; a larger sample may enable the identification of factors that predict improvement or remission of prediabetes or T2DM following LSG. Any definitive conclusions about the effects of LSG on the long-term improvement and remission of prediabetes and T2DM must be deferred until the completion of the larger study.

It should be noted that while the sample size of this study may seem quite small compared to those of the meta-analyses discussed in Chapter 2, examination of the individual studies reveals that the sample size is quite reasonable. For example, the meta-analysis by Wang et al. (2013) has a combined number of 1004 patients in 11 studies; but the individual studies have sample sizes ranging from 20 to 210 with five studies reporting on less than 40 patients each. Furthermore, the meta-analysis by Li et al. (2013) combines 5 studies for a total sample size of 396 patients; however, with the exception of 1 large study with a sample size of 238 patients, the remaining studies had sample sizes ranging from 15 to 60 patients. Thus, the small sample size of the current study appears to be not so small after all, and the larger study will eventually follow more patients than some of the individual studies included in the aforementioned meta-analyses.

6.2 Clinical Implications and Knowledge Translation

The clinical implications for the larger study will be used to inform health care professionals on the benefits of bariatric surgery as a metabolic surgery if patients achieve improvement or remission of diabetes for a prolonged period of time. It can also inform physicians as well as people with T2DM and obesity about another potential treatment option for diabetes particularly for individuals that have challenges controlling their diabetes with medications or lifestyle interventions. Finally, these results will add to current research on LSG from a Canadian health care perspective and could affect the triage process for bariatric surgery by identifying which patients may benefit the most from surgery and who should be offered surgery first.

This work, as part of the NL BaSco Study, was also a part of the Translational Research Program in Bariatric Care (TRPBC), which is a joint initiative of the bariatric surgery clinic at Eastern Health and researchers from Memorial University's Faculty of Medicine and School of Pharmacy. This translational research program made it possible to interact with the multidisciplinary bariatric surgery clinical team as well as policy makers and other researchers involved in bariatric care in NL throughout this study. Study findings were disseminated to the TRBC team via formal presentations at quarterly meetings. An active knowledge translation program resulted in changes to data collection for the clinical and research team via discussions with the primary investigators and the research nurse. While performing an extensive literature review it became evident that the duration of diabetes could be an important factor in predicting the likelihood of patients experiencing remission of T2DM following bariatric surgery. This data was not being collected initially but is now integrated with the standardized abstraction form.

The results of this study have been presented both locally and nationally. Locally, research findings were disseminated through presentations to the TRPBC team, Clinical Epidemiology Seminar Series, the CIHR Research Planning Meeting for the NL BaSco Study, surgery grand rounds at the Health Sciences Centre in Eastern Health, and the Women In Science & Engineering Speaker Series. Study findings were disseminated nationally at the Canadian Society for Epidemiology and Biostatistics Student Conference 2013 in St. John's, NL, the Canadian Obesity Network's 8th Obesity Boot Camp 2013 in Kananaskis, Alberta, the Canadian Obesity Network's 3rd Canadian Obesity Summit in Vancouver, British Columbia, and the Canadian Obesity Student Meeting 2014 in

Waterloo, Ontario. Finally, a manuscript will be prepared for publication and will be submitted to the Canadian Journal of Diabetes for peer review in the fall of 2014.

6.3 Future Research

Future research on the effect of bariatric surgery on prediabetes and T2DM will be increasingly important and relevant as the prevalence of obesity and diabetes continues to rise. Agreeing on standard definitions for improvement and remission of prediabetes and T2DM will be essential for future research. Without a standard definition, it is hard to compare study results and to truly understand the effect of bariatric surgery on prediabetes and T2DM. It is also important to study the effects of bariatric surgery not only on T2DM but also on prediabetes. If it is indeed found that patients with prediabetes are able to achieve normal glycemic measures following bariatric surgery, the incidence of T2DM could decrease and triage for bariatric surgery patients may also change. However, before research in this area can affect health care practices and LSG can be recommended as a treatment for T2DM there is a need for more long-term studies on LSG from a Canadian health care perspective to evaluate the duration of improvement or remission experienced by patients following surgery and explore potential pre-operative predictive factors for remission.

6.4 Conclusions

Patients living with obesity and either prediabetes or T2DM who seek bariatric surgery as a means of losing weight may experience improvements in glycemic control, reductions in antidiabetic medications, or remission of prediabetes or T2DM within the first 12 months post-surgery. Patients may also experience improvements in blood

pressure, and levels of serum triglycerides and HDL. While the results from this study show positive outcomes for patients living with prediabetes or T2DM almost immediately after surgery, more research with larger sample sizes is needed to determine the long-term implications of bariatric surgery on diabetes complications, diabetes prevalence, mortality, etc. before bariatric surgery can be considered as a treatment for prediabetes or T2DM.

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APPENDIX A: Ethical Approval

Health Research Ethics Authority

received MAY 07 2013

Request For Ethics Renewal / Study Closure

- The Tri-Council Policy Statement- Ethical Conduct for Research Involving Humans (TCPS2; 2010) (article 6.14) requires ongoing review by the approving REB at least on an annual basis. The information provided in this form must be current to the time of submission and submitted to the HREA not less than 30 days nor more than 45 days before the anniversary of your approval date.
- Ethics approval is required If there is ongoing subject contact or data collection/transfer is active.
- Ethics approval is not required and the file may be closed If the project is in analysis or the writing stage.
- Please forward a summary of findings or published abstract to the HREA Office once the study is complete.
- Incomplete forms will not be accepted and may result in delay in the review and approval process
- (For clinical trials only) If the project is complete – please submit the applicable Study Closure form.

HREB Ref Number: 11.101	**Expiry Date of Current Approval** 06/08/2013
Principal Investigator: Dr. Laurie Twells	
Title of study (with Protocol Number if applicable): **The Newfoundland and Labrador Bariatric Surgery Cohort Study (The NL BaSco Study)**	
Email of PI : ltwells@mun.ca	**Email of Key Contact:** Kimberley.manning@easternhealth.ca

Please chose one:		
OR	*I am requesting renewal of ethics approval for this file.*	X
	I am requesting to close this file.	

Dr. Laurie Twells
Name typed or printed

Signature of PI

04/29/2013
Date (MM/DD/YYY)

For HREB Office Use Only:

This project was reviewed on May 6, 2013 *Date* *By Full Board Review* ☐ *By Expedited Review* ☑

Ethics approval for this project has been granted for a period of 12 months effective *From* June 9, 2013 *to* June 9, 2014

This research ethics board (the HREB) has reviewed and approved the study which is to be conducted by you as the qualified investigator/principal investigator named above. This approval and the views of this Research Ethics Board have been documented in writing. The Health Research Ethics Board operates according to *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, ICH Guidance E6: Good Clinical Practice: Consolidated guideline* and applicable laws and regulations. The membership of this research ethics board is constituted in compliance with the membership requirements for research ethics boards as defined by Health Canada Food and Drug Regulations Division 5; Part C.

This file has been closed as requested ☐

APPROVED MAY 0 6 2013

Signature Chair *Date*

Recruitment/Data Collection

Has the study started?	Yes	No
	X	

If yes, please provide the following information as it applies to your project.

	Total planned for this site	Total to date *(if applicable)*	N/A
A. Number of Participants enrolled	200	152	
B. Number of Health Records reviewed			X
C. Number of tissue samples collected			X
D. Number of surveys returned			X

If more or fewer than expected, why?

Consent Form

Does this project have a consent form?	Yes	No
	X	

If yes, Please give the date of the most recently approved consent form	06	14	2011

For Clinical Trials Only *which are subject to ICH & Health Canada and required to report SAEs and SUSAR's to the REB*
Serious Adverse Event/s (SAE's) Or Suspected Unexpected Serious Adverse Reactions (SUSARS)

1. **Since Last Approval** a. Have DSMB/ QSR reports been submitted to HREB?	**Yes**	**No**
2. **Since Last Approval** **a.** Has there been amendments to this protocol as a result of safety reports ? *If yes, please provide a list amendment dates*	**Yes**	**No**
3. **Since Last Approval** a. Have you reported local SAE's? b. **If yes**, please provide number of **local** events: _____	**Yes**	**No**
4. **Since Last Approval** a. Have you reported deviations to the sponsor? b. **If yes**, please provide number of **Deviations:** _____	**Yes**	**No**
5. **Since Last Approval** a. Have you requested waivers? b. **If yes**, please provide number of **waivers:** _____	**Yes**	**No**

All Other Studies: Since Last Approval				
1. Have there been unexpected events or problems related to participant risk since original approval or last ethics renewal?	**Yes**		**No**	X
2. Has there been amendments submitted for this project? Approved administrative amendments dated October 11, 2011, February 21, 2012,and May 29,2012.	**Yes**	X	**No**	
If yes, please describe the events/problems/amendments : (Add an addendum to this form if necessary)				

All Studies - Status At Local Site (check all that apply)	YES	NO	N/A
1. Intervention/data collection active	X		
2. Closed to recruitment/accrual		X	
3. Participants in follow up	X		
4. Site closed [clinical trials only]			X
5. **For secondary use of date only** is Data Transfer Complete			X

Knowledge Transfer	YES	NO	N/A
1. Have participants been informed of study findings?		X	
2. Have findings been presented/published? *Please Indicate where: (Add an addendum to this form if necessary)*		X	

Additional Information :