Surgical induced insulin resistance:

Prediction and prevention

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CONTRIBUTION OF AUTHORS

Negar Karimian- Main author of this thesis, developed the original research questions and designed the studies in collaboration with the PhD supervisors, wrote the protocols, recruited patients, performed the experiments, collected the data, interpreted the data and wrote the manuscripts

Liane S Feldman- PhD Supervisor, developed the whole scope of PhD training and original research questions, contributed to design of the studies, interpretation of data, writing and scientific review of manuscripts

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Pepa Kaneva- Performed statistical analysis, contributed to the ethical board submissions and logistics of studies (chapters 2.4, 3.2 and 3.4)

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STATEMENT OF ORIGINALITY

This thesis represents the original and novel research contributing to the field of Enhanced Recovery after Surgery by exploring various strategies to predict and prevent/reduce postoperative insulin resistance mainly in nondiabetic colorectal surgery population.

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LIST OF TABLES AND FIGURES

ABSTRACT:

The surgical stress response results in postoperative insulin resistance and hyperglycemia, both strongly associated with postoperative infections and overall morbidity. As such, identifying patients at higher risk of developing postoperative insulin resistance and hyperglycemia (prediction) and containing the surgical stress response and reducing postoperative insulin resistance and hyperglycemia (prevention) are both essential to reduce postoperative infections and other adverse events. The current dissertation addresses both aspects.

The first part of the thesis addresses the "prediction" aspect through preoperative screening for dysglycemia by measuring HbA1c levels as an indicator of long term glucose control. Nondiabetic patients with underlying degrees of insulin resistance are more prone to develop of postoperative insulin resistance. Therefore earlier diagnosis of dysglycemia and increased glucose monitoring for nondiabetic patients might be as important as for diabetic patients. A systematic review was performed to identify the current evidence regarding the association of preoperative HbA1c with postoperative outcomes in nondiabetic patients. The available evidence was extremely limited; only one study in colorectal patients was found which was in the context of traditional open surgery. However, with current surgical and anesthetic techniques, including widespread use of minimally invasive surgery and Enhanced Recovery Pathways (ERPs), the surgical induced stress response is less pronounced. Therefore, we performed a prospective cohort study to assess the value of preoperative HbA1c screening to predict postoperative infections in nondiabetic patients undergoing elective colorectal surgery within an ERP. No association was found between elevated HbA1c levels and postoperative

infections or other complications. Therefore, preoperative screening with HbA1c is not recommended in this population.

This lack of association between preoperative HbA1c levels and postoperative outcomes in this population might be attributed to the maintained insulin sensitivity seen with laparoscopic colorectal surgery in ERPs. Therefore the question remains whether other recommended preventive interventions to attenuate the surgical stress response and reduce postoperative insulin resistance are still useful in these populations. For example, provision of drinks containing complex carbohydrate (CHO) prior to surgery is strongly recommended in guidelines from the Enhanced Recovery after Surgery Society to reduce postoperative insulin resistance. However, these drinks are not widely available and drinks containing simple CHO are often used in practice. With modern surgical and perioperative care techniques, is this adequate to prevent the insulin resistance that is a classic component of the metabolic response to surgery?

The second part of the thesis addresses the "prevention" aspect by assessing the impact of a simple carbohydrate (CHO) drink on insulin sensitivity. It is known that the insulin response to a drink containing simple CHO would be lower than that triggered by a complex CHO drink. We first assessed the insulin response triggered by simple CHO drinks in healthy volunteers and studied whether the addition of whey protein, an insulinotropic supplement, would result in a higher insulin response. Addition of whey protein was not found to be effective in enhancing the insulin response after simple CHO drinks. However, even if the insulin response to a simple CHO drink is lower than that seen after complex CHO, whether this would impact maintenance of insulin sensitivity in the perioperative setting is not known. Therefore, we compared the impact of simple CHO versus complex CHO on intra and postoperative insulin sensitivity in a randomized controlled trial in nondiabetic patients undergoing elective laparoscopic colon

resection. Unlike in previous studies in open surgery, insulin sensitivity was maintained and there was no difference between the simple and complex CHO drinks. In this setting, we conclude that either drink could be used to prepare patients for surgery.

RÉSUMÉ:

La réponse au stress chirurgical entraîne une résistance à l'insuline postopératoire et une hyperglycémie, deux facteurs fortement associés aux infections postopératoires et à la morbidité globale. En tant que tel, l'identification des patients présentant un risque plus élevé de développer une résistance à l'insuline postopératoire et une hyperglycémie (prédiction), de contenir la réponse au stress chirurgical et de réduire la résistance à l'insuline postopératoire et l'hyperglycémie (prévention) est essentielle pour réduire les infections postopératoires et autres événements indésirables. La thèse actuelle aborde les deux aspects.

La première partie de la thèse aborde l'aspect «prédiction» via le dépistage préopératoire de la dysglycémie en mesurant les taux d'HbA1c en tant qu'indicateur du contrôle de la glycémie à long terme. Les patients non diabétiques présentant des degrés sous-jacents de résistance à l'insuline sont plus susceptibles de développer une résistance à l'insuline postopératoire. Par conséquent, un diagnostic précoce de la dysglycémie et une surveillance accrue de la glycémie chez les patients non diabétiques pourraient être aussi importants que chez les patients diabétiques. Une revue systématique a été réalisée pour identifier les preuves actuelles concernant l'association de l'HbA1c préopératoire avec les résultats postopératoires chez les patients non diabétiques. Les preuves disponibles étaient extrêmement limitées. On n'a trouvé

qu'une seule étude chez des patients atteints de cancer colorectal, dans le contexte d'une chirurgie ouverte traditionnelle. Cependant, avec les techniques chirurgicales et anesthésiques actuelles, y compris le recours généralisé à la chirurgie peu invasive et aux voies de récupération améliorées (ERP), la réponse au stress induit par la chirurgie est moins prononcée. Par conséquent, nous avons effectué une étude de cohorte prospective pour évaluer la valeur du dépistage préopératoire du HbA1c pour prédire les infections postopératoires chez les patients non diabétiques subissant une chirurgie colorectale non urgente dans le cadre d'un ERP. Aucune association n'a été constatée entre les taux élevés d'HbA1c et les infections postopératoires ou autres complications. Par conséquent, le dépistage préopératoire avec l'HbA1c n'est pas recommandé dans cette population.

Cette absence d'association entre les taux d'HbA1c préopératoires et les résultats postopératoires dans cette population pourrait être attribuée au maintien de la sensibilité à l'insuline observée lors de la chirurgie colorectale laparoscopique dans les ERP. La question reste donc de savoir si d'autres interventions préventives recommandées pour atténuer la réponse au stress chirurgical et réduire la résistance à l'insuline postopératoire sont toujours utiles dans ces populations. Par exemple, il est fortement recommandé de prendre des boissons contenant des glucides complexes (CHO) avant une intervention chirurgicale dans les directives de Enhanced Recovery after Surgery Society afin de réduire la résistance à l'insuline postopératoire. Cependant, ces boissons ne sont pas largement disponibles et des boissons contenant du CHO simple sont souvent utilisées dans la pratique. Avec les techniques modernes de soins chirurgicaux et périopératoires, cela permet-il de prévenir la résistance à l'insuline, composante classique de la réponse métabolique à la chirurgie?

La deuxième partie de la thèse aborde l'aspect «prévention» en évaluant l'impact d'une simple boisson glucidique sur la sensibilité à l'insuline. On sait que la réponse insulinique à une boisson contenant de la CHO simple serait inférieure à celle déclenchée par une boisson de CHO complexe. Nous avons d'abord évalué la réponse à l'insuline déclenchée par de simples boissons CHO chez des volontaires sains et avons examiné si l'ajout de la protéine de lactosérum, un supplément insulinotrope, entraînerait une réponse à l'insuline plus élevée. L'ajout de protéines de lactosérum n'a pas été efficace pour augmenter la réponse à l'insuline après de simples boissons CHO. Cependant, même si la réponse insuline à une simple boisson CHO est inférieure à celle observée après une CHO complexe, on ignore si cela affectera le maintien de la sensibilité à l'insuline en situation périopératoire. Par conséquent, nous avons comparé l'impact de la CHO simple par rapport à la CHO complexe sur la sensibilité à l'insuline peropératoire et postopératoire dans un essai contrôlé randomisé chez des patients non diabétiques soumis à une résection élective du côlon par laparoscopie. Contrairement aux études précédentes en chirurgie ouverte, la sensibilité à l'insuline était maintenue et il n'y avait pas de différence entre les boissons CHO simples et complexes. Dans ce contexte, nous concluons que l'une ou l'autre boisson pourrait être utilisée pour préparer les patients à une chirurgie.

CHAPTER 1: INTRODUCTION

1.1 Background:

Postoperative infections impose a significant burden on the health care system and on patient recovery (1). Despite improvements, surgical site infections remain the main cause of morbidity, prolonged hospitalization and death after surgery (2). In Canada, nearly 1 out of 10 readmissions to hospital after surgery is due to infections (3). Colorectal procedures have particularly high rates of postoperative infections, and this is identified as a target for quality improvement (4, 5). Many surgical site infections are considered preventable (6). Identification and correction of risk factors preoperatively as well as implementing a perioperative bundle of interventions are key strategies for prevention (2). These evidence-based best practices can successfully prevent an estimated half of surgical site infections (7). These practices include strategies to reduce the surgical stress response which results in postoperative insulin resistance and hyperglycemia, major factors associated with postoperative infections (8-14).

Surgical stress response:

The surgical stress response is a catabolic state following a cascade of events in the body in response to trauma. This response includes increased secretion of catabolic neuroendocrine hormones including cortisol and catecholamines, activation of the immune system and stimulation of systemic inflammation (15). While this response likely provided a survival advantage to injured animals, in modern surgical practice an excessive surgical stress response results in protein catabolism, delays postoperative recovery and is associated with longer hospital stays (16). The magnitude of the surgical stress response is proportional to the degree of surgical trauma, invasiveness of the procedure, anesthesia and analgesia techniques, blood loss, duration of the surgery, nutritional state and baseline physical activity (17, 18). Insulin resistance is a key

characteristic of the surgical stress response (15), resulting in hyperglycemia. This has been termed the "diabetes of surgery" or "stress hyperglycemia" (19, 20), which can last up to 2-3 weeks postoperatively (21, 22). The peripheral tissue, mainly the skeletal muscle, has been suggested as the main site of postoperative insulin resistance within the first 24 hours after surgery (22, 23).

Postoperative insulin resistance and hyperglycemia:

There are several mechanisms underlying the insulin resistance seen in the surgical stress response, including decreased insulin production in the pancreas, reduced glucose uptake by the peripheral adipose/skeletal muscle tissue through the glucose specific transporter (GLUT4) , and higher glucose production in the liver via gluconeogenesis; these together result in postoperative hyperglycemia (20, 24) (Figure 1).

There is a strong association between insulin resistance, hyperglycemia and postoperative infections, overall complications and longer hospital stay (8-14). Postoperative hyperglycemia is associated with an increased risk of developing postoperative infections (9, 10). This association is even more robust in nondiabetic patients undergoing surgical procedures, compared to patients with known diabetes (4, 13, 25). A large cohort study of 5145 patients undergoing colorectal surgery found that hyperglycemia (> 10 mmol/L) was associated with higher rates of superficial surgical site infections, sepsis and death in nondiabetic patients, but this association was not seen in diabetic patients (4). In another cohort study, more than 66 % of nondiabetic patients undergoing elective colorectal surgery developed hyperglycemia > 7mmol/L and the risk of postoperative infections paralleled the degree of hyperglycemia (25). A study of nondiabetic patients undergoing abdominal, vascular and spine surgery reported a dose response relationship between higher perioperative blood glucose levels from 7mmol/L to > 10mmol/L and

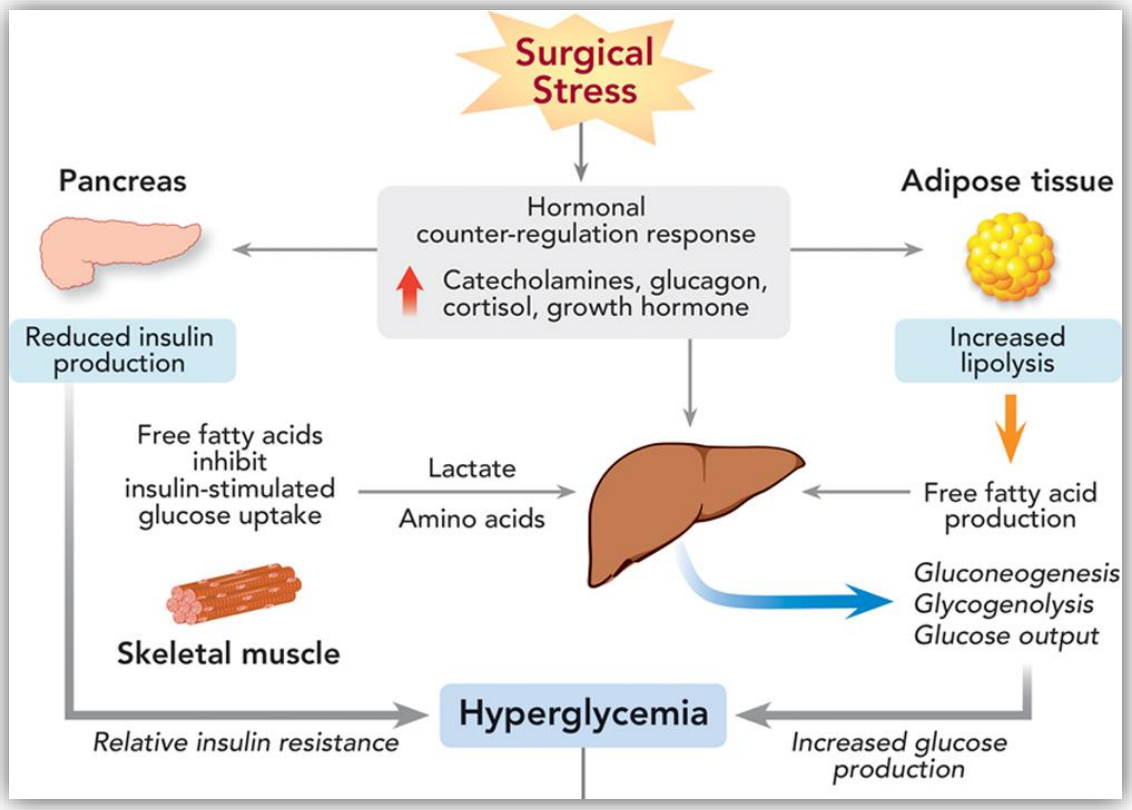
postoperative adverse events, which was not found among diabetic patients. It was speculated that in nondiabetic patients, hyperglycemia is a marker of increased stronger stress.(13). Therefore, effective perioperative glucose control and containing the surgical stress response in order to reduce postoperative infections should be a priority for both diabetic and nondiabetic patents. In a cohort study of 11,633 patients undergoing colorectal or bariatric surgical procedures, 29% of patients developed hyperglycemia (>10mmol/L) in the first 2 days postoperatively; these hyperglycemic patients, regardless of their diabetes status, had increased risk of postoperative infections and reoperations. However, receiving insulin to control perioperative glucose levels reduced the risk of postoperative infections to the same level as patients with normal postoperative glucose levels (26). A recent meta-analysis found that stricter perioperative glucose control protocols with lower target levels of < 8.3 mmol/L were associated with reduced surgical site infections in both diabetic and nondiabetic patients (27).

Postoperative insulin resistance and protein loss:

Loss of body protein is another feature of the postoperative catabolic response. The stress response induced gluconeogenesis in the liver utilizes the gluconeogenic amino acids released by protein breakdown in muscles as important precursors; this has been suggested as one of the major causes of postoperative protein loss (28). The postoperative loss of protein and lean body mass has been linked to impaired immune response, infections, delayed wound healing, muscle weakness, long-term fatigue and decreased vitality (29-32). For example, 15% loss of lean body mass compromises the T-cell mediated immune response leading to delayed wound healing and increased rate of infections (16, 32). Furthermore, the resultant muscle weakness is of serious concern specifically in patients who require mechanical ventilation (16, 32).

Figure 1- Surgical stress response: cascade of events leading to hyperglycemia

Adapted and modified from Elizabeth W. Duggan, et al with permission (33).



HBA1c as a predictor of perioperative insulin resistance/hyperglycemia:

Perioperative hyperglycemia is common with 20%-40% of patients having uncontrolled blood glucose particularly in the first 72 hours after general surgery procedures (33, 34). It has been shown that tight blood glucose control preoperatively reduces the rate of infection and other postoperative complications independent of diabetes (35). Thus, preoperative glycemic control is a priority to improve the quality of surgical care and recovery. Diabetic patients and nondiabetic patients with pre-existing insulin resistance (prediabetes or provisional diabetes) are at greater risk of developing perioperative hyperglycemia (36-38). The prevalence of

undiagnosed/provisional diabetes or pre-diabetes has been reported to vary between 23% to over 60 % in different surgical population (39-45). Therefore, identifying a proper screening test to risk stratify patients according to their preoperative status for development of perioperative insulin resistance and hyperglycemia is essential.

Recently, plasma glycosylated hemoglobin (HbA1c) has been proposed as a screening tool to identify nondiabetic patients with high risk of developing postoperative hyperglycemia and being more prone to postoperative adverse effects (46-49). HbA1c reflects the mean ambient fasting and postprandial glycemia over the preceding 2-3 months (46). The Canadian Diabetes Association (CDA) and American Diabetes Association (ADA) have recommended preoperative HbA1c testing to assess long-term glycemic control in diabetics (40, 50, 51). HbA1c is a useful test for characterizing dysglycemia, is an easier test to perform compared to oral glucose tolerance testing (ie, it is independent of patient prandial status and it does not require the patient to be fasting), and could be done as part of the routine preoperative blood work (46, 52). As defined by ADA guidelines, HbA1c <5.7% is considered normal, while having a plasma HbA1c level of 5.7-6.4% is very high risk for diabetes and in fact carries a 25-50% five-year risk of developing diabetes (50, 51, 53). Finally, an HbA1c $\geq$ 6.5% is diagnostic for diabetes (50, 51). The CDA considers 6% as the cut-off HbA1c level to diagnose pre-diabetes (50, 51). It has been suggested that patients with HbA1c $\geq$ 6% would benefit from receiving an effective intervention such as life style change or receiving glucose lowering medications (54).

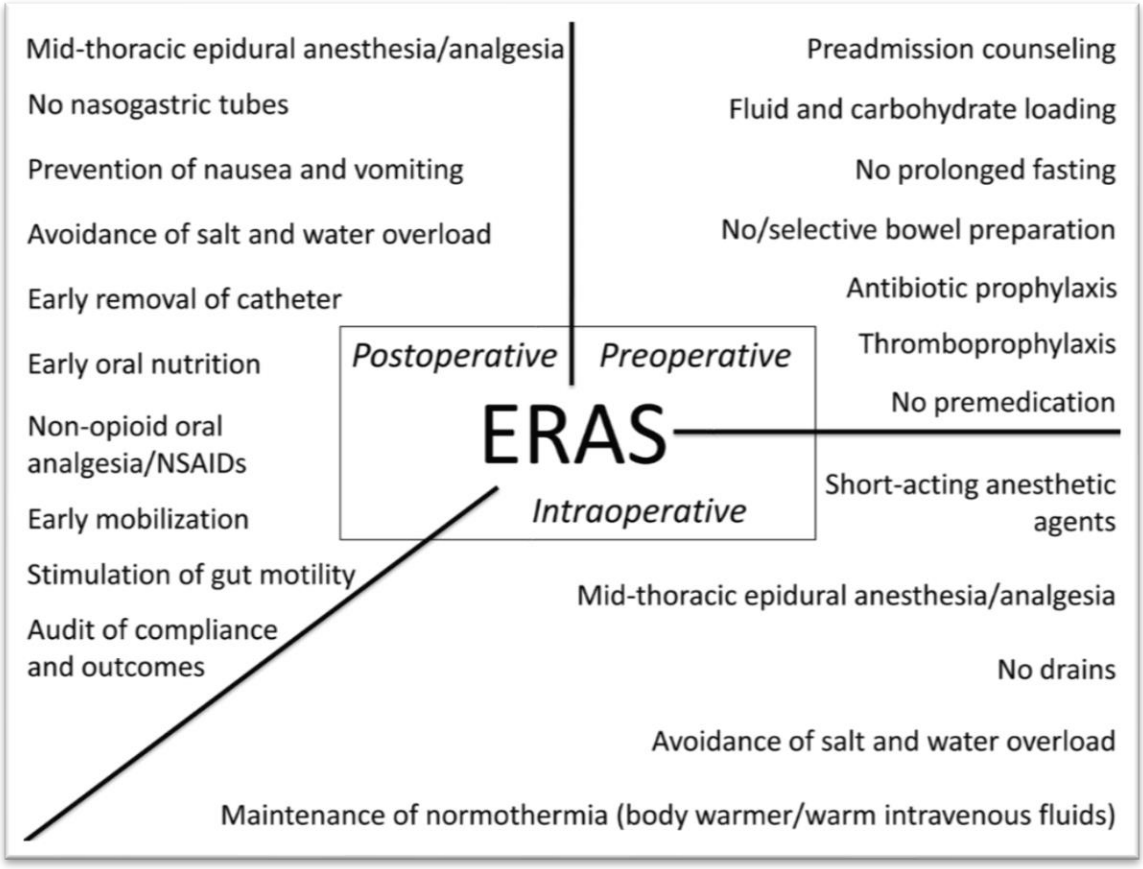
Enhanced recovery pathways (ERP):

Different approaches have been suggested to enhance insulin sensitivity and glucose control in patients undergoing surgical procedures. Enhanced recovery pathways (ERP) are a combination of up to 24 evidence based perioperative interventions to enhance the physical and

functional recovery of patients after surgery by attenuating the magnitude of the surgical stress response (15, 55-57) (Figure-2). In meta-analysis of randomized trials, ERPs result in significant reductions in hospital length of stay and complication rates after a variety of procedures (55). The main perioperative elements of ERPs that contribute to reducing surgically induced insulin resistance, hyperglycemia and protein catabolism include avoidance of preoperative fasting; provision of preoperative carbohydrate (CHO);minimally invasive surgery; neuroaxial blockade with epidural or spinal local anesthetic techniques; maintenance of intraoperative normothermia ; postoperative oral nutritional supplementation; and early postoperative mobilization and physical activity (15).

Figure 2- ERAS elements

Adapted from Varadhan, K. K., et al with permission (57).



Preoperative CHO loading:

Preoperative provision of oral carbohydrate (CHO) drinks is a key element of guidelines from the Enhanced Recovery After Surgery (ERAS) society for optimal perioperative care for colorectal surgery, including the 2019 update (58). Preoperative CHO is also recommended in guidelines from the American Society of Colon and Rectal Surgeons (ASCRS) and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) to improve recovery after colorectal surgery (59, 60). However, the strength of the evidence was graded as low.

The most widely studied CHO drink in this setting contains 12.5% complex carbohydrate maltodextrin (i.e. PreOp®) (24, 61-63) which has been shown to be effective in reducing the postoperative catabolic response, insulin resistance and body protein loss, compared to overnight fasting (24, 61-64). It is suggested that CHO drinks modulate the postoperative insulin sensitivity through enhancing the peripheral tissue glucose uptake which is believed to be the main mechanism of postoperative insulin resistance (15, 22, 65). A recent multicentre trial including over 800 patients demonstrated a reduction in the incidence of hyperglycemia (> 10mmol/L) after preoperative complex CHO loading compared to placebo, with no effect on postoperative infections, complications or length of stay (66). It has been shown that CHO drinks can improve the physiological wellbeing of patients and enhance the "tolerability of surgery" by reducing thirst and hunger preoperatively (67, 68).

In contrast, prominent ERPs in North America mostly use CHO drinks containing simple carbohydrates (i.e. Fructose) such as commercially available fruit juices (69) or sports drinks (eg Gatorade™) for preoperative CHO loading (4, 70). Complex carbohydrates such as maltodextrin have a glycemic index ranging from 85 to 105 compared to simple carbohydrates such as fructose which has a glycemic index of around 19 (71). The glycemic index is an estimate of

how quickly 50 grams of carbohydrate is metabolised in the body (71). Therefore complex carbohydrates trigger a higher insulin secretion response (69) that can block gluconeogenesis in the liver and subsequently reduce the protein breakdown (15). Considering the differences in metabolism of complex versus simple carbohydrates, how fast and to what level they increase the blood glucose level and trigger insulin response (69, 71), it is unknown if simple CHO drinks alone enhance postoperative insulin sensitivity to the same level as drinks containing complex CHO.

There is also limited evidence available regarding whether supplementing simple CHO drinks with other nutritional substances such as protein could augment the insulin response (72, 73). The addition of whey protein, a protein extracted from cow milk, to CHO drinks has also been suggested to modulate the surgical stress response, enhance postoperative insulin sensitivity and reduce postoperative loss of lean body mass (74, 75). It is believed that such effect is the result of the synergetic insulinotropic effect of essential branched chain amino acids such as leucine, isoleucine and valine in whey when added to carbohydrate (76, 77). Whey is also an effective satiating protein which can be beneficial in reducing the hunger prior to operation (78) and enhance patient well-being.

1.2 Thesis objectives:

This thesis addresses the issue of how to predict and modulate perioperative insulin resistance and hyperglycemia from several perspectives. In the first part of the thesis, we addressed risk stratification, specifically focusing on HbA1c measurement, and in the second part we focus on the impact of oral carbohydrate and protein on insulin secretion and insulin sensitivity.

In order to obtain a better understanding of the prognostic value of HbA1C as a risk stratifying strategy, we first performed a systematic review to synthesize previous knowledge of the association of preoperative HbA1c and postoperative complications in nondiabetic patients (Chapter 2.2). Identifying a gap in the literature in colorectal surgery patients, we then performed a prospective cohort study to estimate the impact of elevated preoperative HbA1c on infections after elective laparoscopic colorectal surgery (Chapter 2.4).

In the second part of the thesis, we investigated strategies to modulate perioperative insulin secretion and sensitivity. We focused on interventions related to the use of oral CHO loading, as this is strongly recommended in guidelines for perioperative care, but based on "weak evidence"(58) .

First, we measured the insulin response triggered by a simple CHO drink in healthy volunteers and assessed the impact of the addition of whey protein to simple CHO in enhancing its level of triggered insulin response (Chapter 3.2). We then compared the efficacy of a simple CHO drink compared to a complex CHO drink in enhancing the intra and postoperative insulin sensitivity in a randomized controlled trial (Chapter 3.4).

The specific objectives of this thesis are:

1. To summarize and synthesize the evidence regarding the association between high preoperative HbA1c levels with postoperative complications in nondiabetic adult surgical patients.
2. To estimate the extent to which elevated preoperative HbA1c is associated with postoperative infectious complications in nondiabetic patients undergoing laparoscopic colorectal surgery.

3. To compare the metabolic response to a simple CHO drink versus a simple CHO drink with added whey protein in healthy individuals.
4. To estimate the extent to which ingestion of a preoperative simple CHO drink impacts perioperative insulin resistance in patients undergoing laparoscopic colectomy, compared to a drink containing complex CHO.

CHAPTER 2: PREDICTING AND DIAGNOSING PERIOPERATIVE INSULIN RESISTANCE

2.1 Preamble:

Chapter one reviewed some of the background relating to insulin resistance, hyperglycemia and surgical outcomes. In diabetics previous evidence shows that elevated HbA1c is linked with poorer postoperative outcomes (79) therefore according to the current guidelines known diabetic patients should undergo HbA1c testing preoperatively unless they have a level available within the prior three months (80).

However, association of elevated HbA1c with postoperative outcomes might be even stronger in nondiabetic patients. Elevated HbA1c (>5.7%) is an indicator of chronic dysglycemia (i.e. the last 3 months) and preexisting degrees of insulin resistance i.e prediabetes or provisional diabetes (46). Patients with preexisting insulin resistance are at higher risk of developing stress induced hyperglycemia compared to insulin sensitive patients (36-38). Surgical stress may be more accurately reflected by hyperglycemia in nondiabetics and even one episode of hyperglycemia is associated with an increased risk of adverse events (4, 13, 25). But is hyperglycemia just a marker of surgical stress response or a response to an evolving complication, or can it be predicted preoperatively and therefore potentially modifiable?

In this chapter a systematic review was performed to assess the value of HbA1c as a screening test for preoperative dysglycemia and identify nondiabetic patients at risk for complications.

The manuscript was published in World Journal of Surgery (2018; 42 (1), 61-72). (IF = 2.8)

2.2 Association of elevated preoperative Hemoglobin A1c and postoperative complications in nondiabetic patients: A systematic review

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Abstract:

Importance- Preoperative hyperglycemia is associated with postoperative adverse outcomes in diabetic and nondiabetic patients. Current preoperative screening includes random plasma glucose; yet plasma glycated Hemoglobin (HbA1c) is a better measure of long-term glycemic control. It is not clear whether preoperative HbA1c can identify nondiabetic patients at risk for postoperative complications.

Objective- The systematic review summarizes the evidence pertaining to the association of suboptimal preoperative HbA1c on postoperative outcomes in adult surgical patients with no history of diabetes mellitus.

Evidence review- A detailed search strategy was developed by a librarian to identify all the relevant studies to date from the major online databases.

Findings- A total of six observational studies met all the eligibility criteria and were included in the review. Four studies reported a significant association between preoperative HbA1c levels and postoperative complications in nondiabetic patients. Two studies reported increased postoperative infection rates and two reported no difference. Of 4 studies assessing the length of stay, 3 did not observe any association with HbA1c level and only one study observed a significant impact. Only one study found higher mortality rates in patients with suboptimal HbA1c.

Conclusions and relevance- Based on the limited available evidence, suboptimal preoperative HbA1c levels in patients with no prior history of diabetes predicts postoperative complications and represents a potentially modifiable risk factor.

Introduction:

Preoperative hyperglycemia and insulin resistance are well-established risk factors for post- operative complications in both diabetic and nondiabetic surgical patients (11-14). Insulin resistance and postoperative hyperglycemia are accentuated in diabetic patients (81) as well as nondiabetic patients with some degree of preoperative insulin resistance and/or dysglycemia (36-38). The prevalence of undiagnosed/provisional diabetes and pre-diabetes is unexpectedly high in surgical population, varying from 23% to over 60% (39-45). Perioperative hyperglycemia has been linked to infectious complications and even death in nondiabetic patients (4, 82). As such, a reliable test to screen for dysglycemia and insulin resistance preoperatively is needed.

However, routine preoperative screening does not include a reliable test for diagnosing insulin resistance or dysglycemia. Some practice guidelines recommend random blood sugar (RBS) levels as a preoperative screen for hyperglycemia (83, 84). Although RBS may identify patients with established uncontrolled diabetes, it is highly dependent on the prandial state of the patient and may not identify patients with provisional diabetes or pre-diabetic patients with some levels of insulin resistance who are prone to become hyperglycemic during and after surgery (40). Even a fasting blood glucose test might not be able to identify all patients with dysglycemia before surgery (39).

With these limitations in random blood sugar testing, there is increasing interest in the use of plasma level of glycosylated hemoglobin (HbA1c) to diagnose both dysglycemia and insulin resistance in surgical patients (40). HbA1c is a form of hemoglobin made by non-enzymatic glycation of hemoglobin in exposure to plasma glucose (85). HbA1c is an indicator of long-term (3-4 months) glycemic control (86) and is an excellent measure for diagnosing both

diabetes and pre-diabetes. It does not require the patient to be fasted, is not affected by acute changes in blood glucose levels and is completely independent of the patient's prandial status (87). Thus, it could be used as part of routine screening in the preoperative visit and provide a potentially modifiable risk factor. According to American and Canadian Diabetes Associations guidelines, HbA1c≥6.5% is diagnostic for diabetes and 5.7%≤HbA1c≤ 6.4% is considered pre-diabetes (53, 87).

While HbA1c level has been studied as indicator of poorer surgical outcomes in diabetic patients (88) (89), whether suboptimal HbA1c levels are also associated with higher postoperative hyperglycemia and complications in nondiabetic is unclear (90, 91). The introduction of HbA1c screening requires resources and should be supported by evidence. In this systematic review, we summarize the evidence regarding the correlation of sub-optimized HbA1c levels with postoperative complications in nondiabetic adult surgical patients.

Methods:

Protocol and registration:

This systematic review was conducted based on the PRISMA statement guidelines (92). The review protocol was registered and published on PROSPERO (ID# CRD42015016400) (93).

Search strategy:

A systematic search of bibliographic databases following PICO framework (94) was conducted by a librarian (AA-Z) to retrieve all publications that evaluated preoperative measurement of HbA1C as predictive of any kind of postoperative complication. A search strategy was developed for Medline via OvidSP and peer reviewed by two other hospital librarians. The search was then adapted and run in other databases, including Medline via

OvidSP, on October 20th, 2014: Embase via OvidSP (1947 to 2014 October 17), Biosis via OvidSP (1969 to 2014 week 46), all databases comprising the Cochrane Library via Wiley, CINAHL via Ebsco, Scopus, Web of Science, and Medline via PubMed (for records "as supplied by publisher"), all with no date restrictions. A second hospital librarian also reviewed the adapted search strategies.

The search strategy was designed to retrieve 1) HbA1c and possible variations, 2) preoperative care or the preoperative period, 3) peri- or per- operative care or the peri- or per-operative period, or postoperative care or the postoperative period, 4) surgery, 5) postoperative complications, and 6) risk. All concepts were searched using MeSH or other controlled vocabulary (e.g. Emtree) where available, in combination with text words. The concepts were combined: 1 and 2; or, 1 and (3 or 4) and 5. Both these searches were combined, filtered by the final concept of risk (6), and limited to adult humans. Search strategy details are available in Appendix 1. References from the searches were imported into an EndNote library. Duplicates were removed after all database results were imported.

Eligibility criteria:

The eligibility of the identified observational and cohort studies was evaluated according to the inclusion and exclusion criteria listed in **Table 1**.

Outcome measures:

The main outcomes of interest were 30-day all-cause postoperative morbidity (complications) and mortality. The other studied outcomes were postoperative infection and inflammatory response as well as any procedure-specific complications, length of hospital stay, re-operation and re-admission.

Study selection and data extraction:

Two reviewers (NK and PN) independently assessed the eligibility of bibliographic records. Studies selected after the first screening were retrieved and independently evaluated by two reviewers and conflicts were resolved. After screening, a citation search was performed using Scopus and Web of Science, retrieving articles cited in the selected studies, as well as articles which have cited the selected studies. These articles were subsequently screened.

The Ovid Medline and PubMed (non-Medline) searches were updated on December 20, 2016. The six included studies, all available in Medline, were also checked January 4, 2017 for corrections, errata, retractions or updates. None had been amended.

Risk of bias and quality of evidence assessment:

All the included studies were critically appraised by two separate reviewers (NK and PN) according to the Quality in Prognostic Studies (QUIPS) tool (95). This tool is specifically designed to evaluate risk of bias in prognostic cohort type studies across 6 main domains: (1) study participants (2) study attrition (3) prognostic factor measurement (4) outcome measurement (5) study confounding (6) statistical analysis and reporting. Studies could be rated to have either low, moderate or serious bias across different domains (95). Then we rated the overall evidence by employing Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (96); while GRADE was originally designed to judge the evidence derived from interventional studies, it can also be used to judge the evidence in systematic reviews of prognostic factor studies (97). Based on this framework the level of evidence is judged for each outcome of interest separately; it can be downgraded considering the

studies' limitations, inconsistency, indirectness, imprecision and publication bias and upgraded considering large effect and exposure-gradient responses (97).

Data analysis:

Based on the very diverse populations in the reviewed studies, we were not able to combine their results to conduct a meta-analysis; therefore the results were narratively reviewed.

Results:

Study selection:

4153 studies were retrieved using our search strategy; after removing the duplicates (n = 1620), we screened the abstracts based on the eligibility criteria. Fifty-eight full texts were retrieved for extensive review. Six studies met all the eligibility criteria and remained in the systematic review (Figure 1).

Characteristics of the included studies:

The included studies had either low or moderate risk of bias across different domains according to the QUIPS tool (95) (Table 2) . Three out of six studies were prospective observational studies while the other three were retrospective. Overall, a total of 14,363 nondiabetic patients undergoing various types of surgeries were included in the studies; 34% of these patients (n= 4898) had sub-optimized HbA1c prior to surgery as defined most commonly as HbA1c $\geq$ 6% (Table 3). Three of the six studies (90, 91, 98) did not define an upper limit for HbA1c as an exclusion, defining nondiabetic patients as those without diet/pharmacologically controlled diabetes (98), and/or having fasted glucose levels below 7 mmol/L(90, 91). The results from the included studies will be summarized in the following categories: 30-day

postoperative complication/morbidity, postoperative infection, 30-day mortality, length of stay, re-operation and re-admission. The overall strength of the existing evidence for each outcome has been summarized in Table 5 using the GRADE framework.

Postoperative complications /morbidity:

Four out of six studies reported 30 day postoperative complications and overall morbidity (90, 91, 98, 99)(Table 4). All had low risk of bias. Two of them were prospective observational studies on colorectal surgery (98) and vascular surgery patients (90); the other two were both retrospective observational studies on collected data from large prospectively maintained databases of cardiac surgery (91) and laparoscopic gastric bypass surgery patients (99). All four studies showed some degrees of association between sub-optimized levels of HbA1c and postoperative overall complication rate or specific procedure-related complications. In the colorectal surgery study, after adjusting for different confounders, the authors observed a threefold increase risk of overall postoperative complications. This was mainly due to pneumonia, urinary tract infection, pleural effusion and postoperative ileus (45% vs 25%, adjusted OR=2.9, 95%CI=1.1-7.9, p=0.037) (98).

Sullivan et al. observed that the nondiabetic vascular surgery patients with suboptimal HbA1c had a significantly higher all-cause 30 day morbidity compared to the normal Hba1c group (56.5% vs 15.7%,95% CI = 2.8-17.2, RR=7, p<0.001); when categorized based on the procedures, more specifically, they observed significant differences in nondiabetic patients with suboptimal HbA1c undergoing aortic procedures (50% Vs 6.7%; p=0.009) and peripheral arterial procedures (77.8% Vs 20%; p= 0.003)(90). Among the cardiac surgery patients, the risk of acute kidney injury was higher in patients with elevated HbA1c levels even after adjusting for other known renal risk factors (Adjusted OR=1.148,95%CI=1.003-1.313 p=0.04)(91). Among

the nondiabetic gastric bypass patients, Stenberg et al. observed that suboptimal HbA1c was associated with having any postoperative complication (OR 1.16, 95%CI=1.00-1.33, p=0.043) and a severe (≥3b Clavien- Dindo (100)) postoperative complication (OR=1.3, 95%CI= 1.05-1.61, P =0.012), which remained after adjusting for confounding factors (Adjusted OR=1.26, 95%CI=1.01-1.59, p=0.042). More specifically, higher HbA1c was associated with increased risk of pulmonary complications (OR=1.92, 95%CI=1.17-3.14, p=0.009), and small bowel obstruction/prolonged ileus (OR=1.55, 95%CI=1.09-2.22, p=0.016) (99).

Postoperative infection:

Three studies with low risk of bias reported the rate of postoperative infection among cardiac, colorectal and vascular surgery patients (90, 91, 98) and one study reported the risk of leakage and abscesses among the nondiabetic gastric bypass patients (99). Three out of 4 studies did not see any association between rate of postoperative infection and the pre- operative level of HbA1c, while only one found a significant association in their study populations (Table 4). While the 30-day postoperative infection rate was increased in the higher preoperative Hba1c subgroup, this did not reach statistical significance among the nondiabetic colorectal surgery patient (29% versus 17%, adjusted OR 2.3, 95%CI=0.8-5.2, p= 0.129)(98). Likewise, among the nondiabetic patients undergoing laparoscopic gastric bypass, while higher HbA1c was associated with increased risk of anastomotic leakage/abscess, this did not reach statistical significance (OR=1.33, 95%CI 0.98-1.82,p= 0.071) (99). In addition, in the study on the cardiac surgery patients, no association was observed between postoperative infection and elevated HbA1c levels (p=0.48) (91). Only, O'Sullivan et al. documented an overall higher incidence of overall postoperative infection (21.1% vs 5.9%, p=0.037), specifically surgical wound infection (9.9%

vs 0%, p<0.05) among nondiabetic patients with sub-optimized HbA1c levels undergoing vascular surgery (90).

Mortality:

Two of the included studies with low risk of bias reported 30 day mortality as their primary outcome (90, 91)(Table 4) . One in vascular surgery patients did not find any significant difference in all cause 30 day mortality between the nondiabetic patients with higher than normal HbA1c and with normal HbA1c (6%<HbA1c< 7% Vs HbA1c ≤ 6%)(90). In a second study in cardiac surgery patients, HbA1c>6 % in nondiabetic patients was independently associated with increased risk of 30 day mortality i.e. 53% increase in the risk of early postoperative mortality per percent increase of HbA1c level (OR 1.53; 95% CI+1.24-1.91, p=0.0005; similar results were found even after excluding the borderline diabetic patients (with fasting blood glucose >7mmol/l) (p=0.05) (91).

Length of stay:

Four of the included studies compare length of stay in nondiabetic surgical patient population stratified by preoperative HbA1c levels (Table 4). None of the three prospective observational studies in colorectal (98), cardiac (101) and vascular (90) surgery patients found any association between levels of pre-op HbA1c and length of stay (90, 91, 98, 101). Only the retrospective study on spine surgery patients observed that LOS and total cost (hospital and physician) was significantly higher in nondiabetics with HbA1c > 6.1 compared to nondiabetics with normal HbA1c (<6.1%)(44).

Re-operation and re-admission:

None of the included studies included re-operation or re-admission rates as outcomes.

Discussion:

The purpose of this systematic review was to summarize the available evidence to better understand whether preoperative level of HbA1c in the nondiabetic adult surgical patients is an indicator of increased risk for postoperative adverse outcomes. This is a critical question to address prior to evaluating the candidacy of HbA1c as a potential screening test preoperatively. In synthesizing the available data on 14,363 patients without previously diagnosed diabetes undergoing various types of surgeries we found that high preoperative HbA1c (generally defined as >6%) was associated with higher risk of overall postoperative complications after colorectal, bariatric, vascular and cardiac surgery.

We specifically addressed the prognostic value of preoperative HbA1c screening in patients without previously diagnosed diabetes. A previous systematic review reported an association of high preoperative glucose and HbA1c levels with increased postoperative complications (102); however, this review also included diabetic patients. The HbA1c levels of a diabetic patient who is receiving pharmacological treatment might be as low as the levels of a nondiabetic individual, however, similar HbA1c levels do not necessarily reflect the same metabolic status. The increased risk of postoperative complications in studies with mixed population could be attributed to diabetes status and not to HbA1c level alone (102) and the review concluded that neither blood glucose testing nor HbA1c screening was recommended for non- diabetic patients, except for procedures where there is a high prevalence of undiagnosed diabetes e.g. vascular and orthopedics surgery.

In the studies included in the present review, higher levels of HbA1c were seen in patients with higher BMI and older age and were regarded as confounding factors adjusted for in

the statistical analysis (91, 98, 99). These are well-defined risk factors for the development of perioperative complications (103-106). A state of increased insulin resistance, as identified by higher HbA1c levels, could accentuate the surgery induced metabolic stress in this population and further complicate or slow their recovery after surgery. Therefore, it might be particularly beneficial to target these patients for HbA1c screening prior to surgery.

Preoperative HbA1c screening can help identify patients with undiagnosed diabetes as well as pre-diabetic patients and can differentiate patients with stress hyperglycemia (40, 42). Undiagnosed diabetes has been suggested to represent a much higher risk factor for postoperative complications than known diabetic state (107, 108). In US alone, the overall prevalence of pre-diabetes in 2011-12 was estimated to be 38%; the same data also indicated that among the diabetic population in US, up to 36% were undiagnosed (109). Both diabetes and pre-diabetes may result in some degrees of insulin resistance (53) which may warrant preoperative physiological conditioning and/or pharmacological interventions as well as closer postoperative glucose monitoring and control (110-112). Higher preoperative HbA1c levels are associated with postoperative hyperglycemia and possible need for insulin infusion among nondiabetic patients (36, 91, 98, 113). As insulin resistance is a central feature of the metabolic response to surgery, identification of interventions that preserve insulin sensitivity is a key strategy to improve outcomes (15). Regardless of diabetes status, a 20% increase in insulin resistance was associated with a more than two-fold increase in the risk of serious complications after cardiac surgery (14).

The four studies that investigated postoperative complication/ morbidity were all consistent in observing strong associations between higher levels of HbA1c (>6%) and elevated rate of postoperative complications. Based on GRADE approach (Table 5), the strength of evidence regarding this finding is at high level because for prognostic studies, retrospective and

prospective cohorts could be the best approach to investigate the association between the prognostic factor and outcomes (97). Furthermore, the large effects observed in at least two of the included studies and the gradient response of HbA1c levels in relation to postoperative outcomes contribute to upgrading the evidence (97).

Postoperative infections are among the most resource consuming and costly complications after surgery, contributing to longer hospital stays, readmissions and emergency visits (114, 115). Perioperative hyperglycemia is a risk factor for postoperative infections (12, 45, 116). Postoperative hyperglycemia was associated with superficial site infections, sepsis and even death in nondiabetic patients undergoing colorectal surgery (4). Hence, an efficient screening tool for preoperative hyperglycemia such as plasma HbA1c could play an important role in preventing postoperative infections by identifying nondiabetic patients who may benefit from monitoring and treatment of hyperglycemia. Yet the data from the few studies reporting postoperative infections was conflicting, with an increase rate of infection in the nondiabetic vascular surgery patients with high preoperative HbA1c (90), a trend towards increased infections and risk of anastomotic leakage/abscess in patients with suboptimal HbA1c undergoing colorectal surgery (98) and gastric bypass surgery (99), but no increased risk in cardiac surgery patients (91).

Recently preoperative HbA1c screening has been included in the 2014 draft of best practices for perioperative glucose control from Strong for Surgery which issues guidelines for perioperative care in Washington State. Although, it is unclear whether optimization of patients with poorly controlled diabetes improves outcomes, this guideline recommends screening all diabetic patients and patients at risk for diabetes or pre-diabetes (i.e. age $\geq$ 40 or BMI $\geq$ 30) by HbA1c or fasting blood glucose prior to surgery (117). Other major guidelines also recommend

testing for HbA1c in all diabetic patients (118, 119) however, they have not recommended HbA1c screening as the initial test to diagnose dysglycemia in the preoperative visit for people without diabetes (118, 119). These guidelines instead recommend random blood glucose testing (83, 84, 118, 119). However, this test is highly dependent on prandial state of patients and high rates of false negatives in diagnosing pre-diabetes and diabetes makes it inappropriate as an efficient screening tool for preoperative dysglycemia (40); more importantly, it results in missing the patients with dysglycemia who could benefit from better perioperative monitoring and control of blood glucose.

What is attractive about HbA1c screening is the potential to intervene and improve outcomes. In a risk predictive model study on cardiac surgery patients reduction of HbA1c from 8% to 5.5% predicted reduction in LOS by almost half a day; this suggest HbA1c as modifiable risk factor (120). Upon diagnosis of preoperative dysglycemia and /or insulin resistance by suboptimal HbA1c levels, various pharmacologic or physiologic interventions could be reinforced in order to modify the risks associated with these conditions. These interventions could include but are not limited to preoperative diet modification, exercise and administration of insulin sensitizers. Perioperative glucose control by insulin administration decreased renal complications in nondiabetic cardiac surgery patients (121) and overall mortality and morbidity in surgical patients at intensive care unit.(122). Perioperative glucose control has been also recommended for prevention of surgical site infections (123).

This review has several limitations. The restricted number of eligible studies included in this review and the diverse study populations limit the strength of the conclusions and recommendations for some of the outcomes. Therefore, there is need for more studies focusing on the association of sub-optimal HbA1c with these postoperative outcomes in nondiabetic

patients and whether this represents a therapeutic target in order to reduce hyperglycemia and complications in this at-risk population. In some of the included studies considering a higher than 6.5 % upper limit for categorizing the patients with suboptimal HbA1c might have resulted in including some undiagnosed diabetic patients in the non- diabetic category. Therefore, for future studies giving more attention to this matter is warranted. Furthermore, plasma HbA1c is a lab-test which is subject to significant lab-to-lab variation and variation over time. This may impact the utility of a single HbA1c value especially in the preoperative period. Thus, it might be a good practice to couple this measure with another measure such as random or fasting blood sugar level to screen for dysglycemia in nondiabetic patients with risk factors such as advanced age or obesity. In addition, it should be noted that short term interventions cannot modify HbA1c levels and this limits the value of HbA1c as modifiable risk factor in preoperative settings.

In summary, HbA1c is a practical and informative test for screening nondiabetic patients prior to surgery for dysglycemia, prediabetes and undiagnosed diabetes who are at risk of developing postoperative hyperglycemia. The association of suboptimal HbA1c levels >6% with postoperative hyperglycemia and complications highlights its value for risk stratification prior to surgery. Furthermore, suboptimal HbA1c levels may identify patients who may benefit from more intensive monitoring and treatment of perioperative hyperglycemia. However, whether suboptimal preoperative HbA1c represents a modifiable risk factor requires further study.

Conclusion:

The current evidence suggests that elevated preoperative HbA1c levels among patients without prior diagnosis of diabetes might be associated with an increased risk of postoperative

complications. Future studies are essential to assess this possible association and to further explore HbA1c as a modifiable preoperative risk factor.

Acknowledgements:

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Figure1: PRISMA flow diagram (flow of information through the phases of the systematic review).

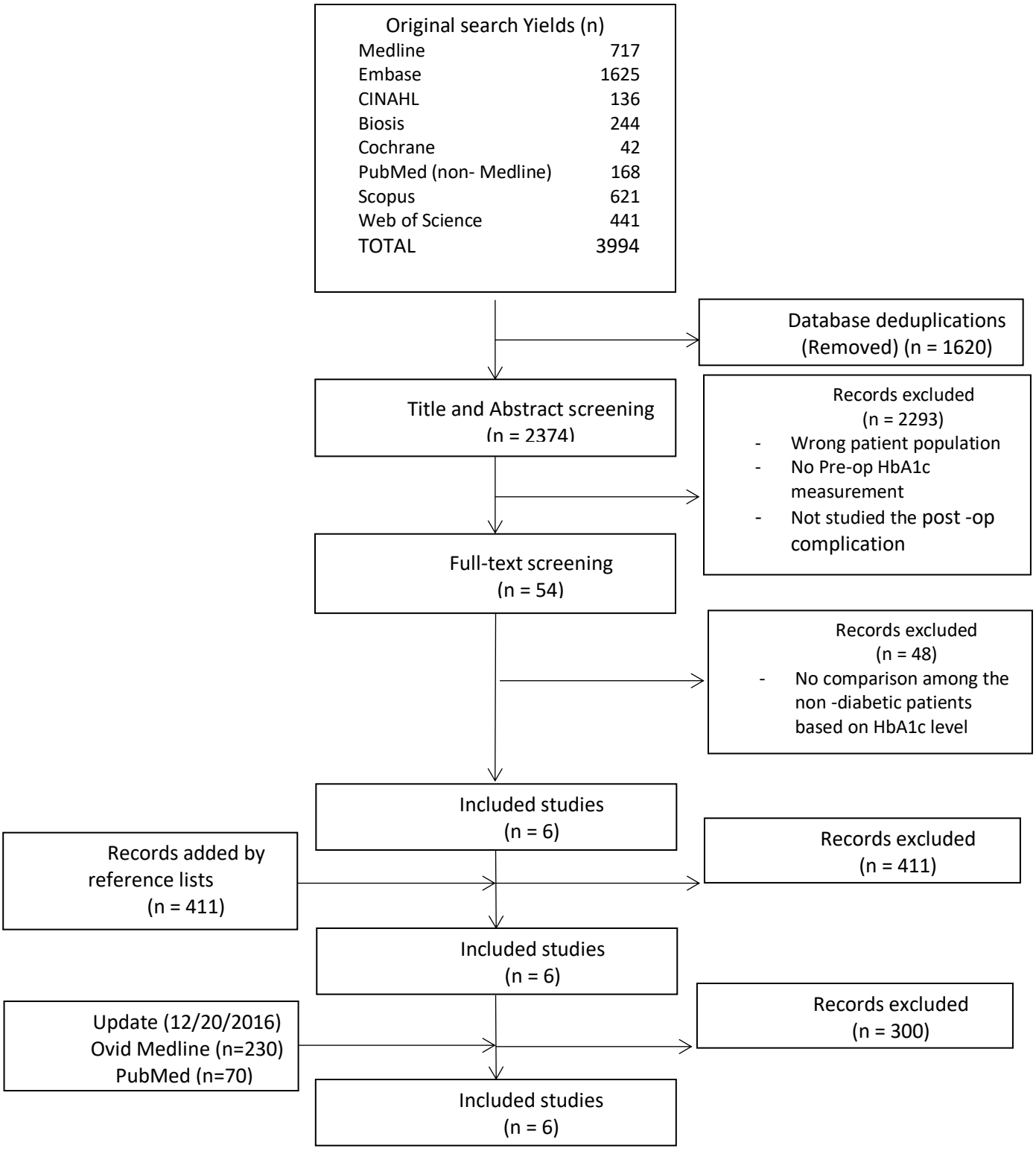

Table 1- Eligibility criteria

Inclusion criteria	
Types of studies	All published observational cohort and case-control studies to date
Types of participants	Over 18 year old Individuals with pre-diabetes or no known history of confirmed diabetes who have undergone any type of surgical procedure and have documented preoperative HbA1c levels
Primary and secondary outcome measures	Postoperative complications, inflammatory response, infection and procedure specific complications, mortality and morbidity within 30 days after surgery related to the surgery, duration of hospital stay, re-operation and re-admission.
Exclusion criteria	
Types of studies	Systematic reviews and conference abstracts
Types of participants	A mixed population of diabetic and nondiabetic surgical patients without sub-analysis of results specific to the nondiabetic cohort
Primary and secondary outcome measures	long-term outcomes after surgery, prognosis or survival

Table 2- Risk of Bias for included studies

Quality in Prognostic Studies (QUIPS)						
Study ID	**Study participation**	**Study Attrition**	**Prognostic Factor Measurement**	**Outcome Measurement**	**Study Confounding**	**Statistical Analysis and Reporting**
Gustafsson et al. 2009 (98)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Hudson et al. 2010 (91)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Medhi et al. 2001(101)	Low risk	Low risk	Low risk	Low risk	Moderate risk	Moderate risk
O'Sullivan et al.2006 (90)	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk
Stenberg et al. 2014 (99)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Walid et al., 2010 (44)	Low risk	Low risk	Low risk	Moderate risk	Moderate risk	low risk

Table 3- Summary of the eligible studies

Study ID and year	Design of the study	Number of nondiabetics (%)	Nondiabetics with suboptimal HbA1c (%)	Patient population (N)	Primary outcome	Secondary outcomes	Results (suboptimal HbA1c Vs normal HbA1c)
Gustafsson et al. 2009 (98)	Prospective observational	120	31(28.5 %)	Nondiabetics, colorectal surgery (120)	Overall post-op and 30 –day complications+	Post-op hyperglycemia, post-op inflammatory response and recovery*, LOS, rate of post-op infection	HbA1c> 6% Vs HbA1c ≤ 6% ↑ post-op complication (adjusted OR =2.9 p= 0.037), no difference in infection rate (adjusted OR= 2.3 P=0.129), ↑ post op hyperglycemia (p=0.012) , no increase in LOS (p=0.482)
Hudson et al. 2010 (91)	Retrospective observational (prospectively collected data)	1474	456(31%)	Nondiabetics, cardiac surgery (1474)	30-day mortality	Post-op acute kidney injury and infection	HbA1c> 6% Vs HbA1c ≤ 6% ↑ post-op 30-day mortality (OR =1.53,p= 0.0005), ↑ post-op acute kidney injury (OR=1.148,p=0.04), no association with post op infection rate (p=0.48)
Medhi et al. 2001(101)	Prospective observational	83(61.4 %)	26(31.3 %)	Diabetics and nondiabetics, CABG surgery (135)	LOS	-	HbA1c> 6% Vs HbA1c ≤ 6.9% No increase in LOS (data not reported)
O'Sullivan et al.2006 (90)	Prospective observational	122(73. 9%)	71(58.2 %)	Diabetics and nondiabetics, vascular surgery (165)	All cause 30-day and 6 month mortality and morbidity	Procedure specific complications, stroke, adverse cardiac events, infection, LOS	6%<HbA1c< 7% Vs HbA1c ≤ 6% ↑ incidence of all cause 30-day morbidity(RR=7, p=0.001), no difference in mortality, ↑incidence of post-op adverse cardiac events in aortic procedures(p=0.012),↑incidence of overall post-op infection(p=0.037) and post-op wound infection (p<0.05), no difference in LOS, stroke and other procedure specific complications, 6%<HbA1c< 7% predicts 30 Day morbidity in nondiabetic patients(OR=10.86,

							p<0.001)
Stenberg et al. 2014(99)	Retrospective observational (prospectively collected data)	12,244(95%)	4,204(32%)	Diabetics (without pharmacologic treatment) and nondiabetics, Laparoscopic Gastric bypass surgery (12,850)	Severe 30 day complication (≥3b Clavien-Dindo)	Specific complications °	5.7%<HbA1c< 6.49% Vs HbA1c ≤ 5.7% ↑risk of severe post-op complication (OR=1.26, adjusted p=0.042), ↑risk of any post-op complication (OR=1.16, p=0.043). For HBA1c ≥6.5%↑risk of Leakage/abscesses, Bleeding, pulmonary complication, cardiovascular complication
Walid et al., 2010 (44)	Retrospective observational	320(72.4%)	(110)14.3%	Diabetics and nondiabetics, Spine surgery (442)	LOS	Total cost	HbA1c≥6.1% Vs HbA1c < 6.1% ↑in LOS and total cost only in LDF subgroup (p<0.05) ,no difference among LMD and ACDF≠

+ Respiratory failure, plural fluid, cardiac failure, cardiac arrhythmia, post-op bleed, post-op ileus, anastomotic leak, stoma necrosis, wound infection, pneumonia, sepsis, urinary infection, other infection
*Postoperative Inflammatory response and recovery : C-reactive protein adjusted P = 0.008 Time to oral food only(no drips) adjusted P = 0.013, time to first bowel movement, Time to epidural anesthesia removal, length of stay and time to fulfill discharge criteria
°Leakage/abscesses, bleeding, small bowel obstruction/prolonged ileus, anastomotic stricture, stromal ulcer, wound dehiscence, port related complication, venous thromboembolism, urinary tract infection, pulmonary complication, cardiovascular complication
≠ LDF: lumbar decompression and fusion subgroup, LMD: lumbar microdiscectomy, ACDF: anterior cervical decompression and fusion

Table 4- Summary of results categorized by the eligible studies

	Gustafsson et al. 2009 (98)	**Hudson et al. 2010** (91)	**Medhi et al. 2001**(101)	**O'Sullivan et al.2006** (90)	**Stenberg et al. 2014** (99)	**Walid et al., 2010** (44)
Post-op complications /morbidity	↑ post-op complication (adjusted OR =2.9 p= 0.037	↑ post-op acute kidney injury (OR=1.148,p=0.04)	N/A	↑ incidence of all cause 30-day morbidity(RR= 7, p=0.001)	↑ risk of any post-op complication (OR=1.16, p=0.043)	N/A
Post-op infection	no difference in infection rate (adjusted OR= 2.3 P=0.129)	no association with post op infection rate (p=0.48)	N/A	↑ incidence of overall post-op infection(p=0.037) and post-op wound infection (p<0.05),	↑ risk of Leakage/ abscesses	N/A
Mortality	N/A	↑ post-op 30-day mortality (OR =1.53,p= 0.0005)	N/A	No difference in mortality	N/A	N/A
Length of stay	No increase in LOS	N/A	No increase in LOS	No increase in LOS	N/A	↑ in LOS only in LDF subgroup (p<0.05)

Table 5- Quality assessment using GRADE approach

Quality assessment							Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		
Postoperative complications /morbidity (follow-up 30 days) (90, 91, 98, 99)								
4	observational studies[1]	no serious risk of bias[2]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	strong association[4] dose response gradient[5]	⊕⊕⊕⊕ HIGH	CRITICAL
Postoperative infection (follow-up 30 days) (90, 91, 98)								
4	observational studies	no serious risk of bias[2]	serious[6]	no serious indirectness	no serious imprecision	dose response gradient[5]	⊕⊕OO LOW	CRITICAL
Mortality (follow-up 30 days) (90, 91)								
2	observational studies	no serious risk of bias[2]	serious[7]	no serious indirectness	no serious imprecision	dose response gradient[5]	⊕⊕OO LOW	CRITICAL
Length of stay (44, 90, 98, 101)								
4	observational studies	serious[8]	no serious inconsistency [9]	no serious indirectness	no serious imprecision	dose response gradient[5]	⊕⊕OO LOW	IMPORTANT
Re-operation and re-admission								
0	No evidence available					none		

[1] Two prospective observational cohort studies and two retrograde cohorts using very large prospectively collected databases
[2] The overall risk of bias for these studies have been rated the lowest as assessed by QUIPS (Quality in prognostic studies tool)

for observational prognostic studies

[3] The included studies on different surgical populations, however all are major surgical procedures with considerable risks of postoperative complications. All 4 studies are consistent in some degree of increase in the overall postoperative complications/ morbidity in the patients with higher than 6% HbA1c

[4] At least two studies with very high effects sufficient to upgrade the level of evidence suggest that patients with suboptimal HbA1c had a significantly higher all-cause 30 day morbidity/postoperative complications compared to the normal Hba1c group : The study on colorectal patients(OR =2.9, 95% CI= 1.1-7.9) ;among vascular surgery patients (RR=7, 95% CI = 2.8-17.2); Gastric bypass patients(OR 1.26, 95%CI1.01-1.59);cardiac surgery patients (OR=1.148,95%CI=1.003-1.313)

[5] In all the studies the nondiabetic patients with higher HbA1c levels of more than 6% have been compared to the nondiabetic patients with HbA1c levels under 6%

[6] There is inconsistency between the reported results from 4 studies. Significant increase in surgical infection in vascular surgery patients with elevated HbA1c as well as the same trend in colorectal and gastric bypass patients; however among the cardiac surgery patient, no association was observed.

[7] There is conflict between the two studies results. There was no significant association between higher HbA1c and mortality in nondiabetic vascular patients while HbA1c >6% was an independent predictor of 30 days mortality among cardiac patients (OR 1.53; 95% CI1.24-1.91, p=0.0005)

[8] One study with moderate risk of bias and three with low risk of bias

[9] Among 4 studies, only one observed significant association between higher HbA1c and length of stay in the hospital inconsistent with the other three which observed no association.

Appendix 1- Ovid Medline search

1. Hemoglobin A, Glycosylated/

2. Hemoglobins/

3. limit 2 to yr="1963 - 1975"

4. Hemoglobin A/

5. limit 4 to yr="1975 - 1983"

6. ((glycat* or glycosylat*) adj2 (hemoglobin* or haemoglobin* or hemo-globin* or haemoglobin*)).tw,kf.

7. (hba1c or "hb a1c" or hbaic or "hb aic").tw,kf.

8. ((ic or 1c or aic or a1c) adj2 (hemoglobin* or haemoglobin* or hemo-globin* or haemoglobin* or hb or hba)).tw,kf.

9. (glycohemoglobin* or glyco-hemoglobin* or glycohaemoglobin* or glycohaemoglobin*).tw,kf.

10. 1 or 3 or 5 or 6 or 7 or 8 or 9

11. exp Preoperative Care/

12. exp Preoperative Period/

13. (pre-op* or preop*).tw,kf.

14. (presurg* or pre-surg*).tw,kf.

15. ((before or prior or previous or undergoing) adj3 (surger* or surgic* or procedure*)).tw,kf.

16. 11 or 12 or 13 or 14 or 15

17. exp Perioperative Care/

18. Perioperative Period/

19. (perop* or per-op* or periop* or peri-op*).tw,kf.

20. Postoperative Period/

21. (postoperati* or (post adj2 operati*) or postsurg* or ((post or after or following) adj2 surg*) or posttransplant* or ((post or after or following) adj2 transplant*) or ((postdischarg* or post-discharg*) adj3 surg*)).tw,kf.

22. or/17-21

23. exp General Surgery/

24. exp Surgical Procedures, Operative/

Appendix 1- Ovid Medline search (continued)

25. (surger* or surgic*).tw,kf.
26. su.fs.
27. or/23-26
28. exp Postoperative Complications/
29. (Co or mo).fs.
30. (morbi* or mortalit* or adverse outcome* or complicat*).tw,kf.
31. 28 or 29 or 30
32. 10 and 16
33. 10 and (22 or 27) and 31
34. 32 or 33
35. "Predictive Value of Tests"/
36. Reference Values/
37. Forecasting/
38. Prognosis/
39. exp risk/
40. (risk or risks or prognos* or predict*).tw,kf.
41. or/35-40
42. 34 and 41
43. Animals/ not (Animals/ and Humans/)
44. 42 not 43
45. (exp child/ or exp infant/ or adolescent/) not exp adult/
46. 44 not 45
47. Remove duplicates from 46

2.3 Preamble:

The systematic review (Chapter 2.2) indicated that there might be an association between elevated preoperative HbA1c levels and postoperative complications in nondiabetic patients. While the colorectal surgery population are at particular high risk of developing postoperative infections (4, 5), the existing evidence for preoperative screening with HbA1c in this population is extremely limited. In fact, only one study included in the systematic review focused on colorectal patients, and found an increased risk of overall postoperative complications but no significant increase in postoperative infections (98) . This study had several limitations: it only included patients undergoing open colorectal surgery, used a high cutoff level of 6% to define elevated HbA1c, and did not exclude patients with undiagnosed diabetes (HbA1c over 6.5%), in whom screening is already recommended (98).

In addition, the previous study included patients having traditional perioperative care. Enhanced Recovery Pathways (ERPs) include multiple interventions to reduce the overall surgical stress response such as using minimally invasive laparoscopic procedures instead of open surgeries. Since in this context the surgical stress response may already be reduced, it is important to define the specific value of screening tests for hyperglycemia in order to avoid additional nonessential costs to the healthcare system and burden to patients. As such, to address the limited existing evidence regarding the association of elevated preoperative HbA1c values and postoperative infections in elective laparoscopic colorectal surgery patients within an ERP, we performed a prospective cohort study.

This manuscript is under review at Diseases of the Colon and Rectum (IF =3).

2.4 Preoperative Level of Hemoglobin A1c Is Not Associated With Postoperative Infections Among Nondiabetic Patients Undergoing Laparoscopic Colorectal Surgery

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Abstract

Background- Perioperative hyperglycemia is associated with increased postoperative infections. HbA1c is a marker of long-term glucose control and an established indicator of poorer outcomes in diabetics. However, whether preoperative HbA1c levels are associated with postoperative complications in nondiabetic patients is unclear. The purpose of the study was to estimate the extent to which elevated preoperative HbA1c is associated with postoperative infectious complications in nondiabetic patients undergoing laparoscopic colorectal surgery in an Enhanced Recovery Program.

Methods- Consecutive patients undergoing elective laparoscopic colorectal surgery for benign and malignant conditions who were screened for a randomized controlled trial requiring preoperative HbA1c levels were included. Elevated HbA1c was defined as HbA1c≥5.7%. Patients with known diabetes were excluded. The primary outcome was overall infectious complications occurring within 30 days of surgery, including incisional surgical site infection (SSI), organ space SSI, urinary tract infection (UTI) pneumonia and/or sepsis. Complications were defined as per NSQIP. Secondary outcomes were pre and postoperative random blood glucose, hospital length of stay, 30-day overall complications and 30-day readmissions rate.

Results- A total of 88 patients with preoperative HbA1c were identified (mean (SD) age 59.5(15.6) years, BMI 25.9(5.2) mg/kg^2, 45% female); when grouped according to preoperative HbA1c levels, 51 patients (48 %) had HbA1c < 5.7% while 37 patients (34%) had 5.7 %≤HbA1c< 6.5% (pre-diabetes/provisional diabetes). There were no differences between the normal and elevated HbA1c groups in 30-day overall infections (3 (6%) vs 1 (3%), p= 0.63), incisional SSI (2 (4%) vs 1 (3%), p= 1), organ space SSI (1 (2%) vs 0, p= 0.4), UTI (1 (2%) vs 0,

p=1) or pneumonia (1 (2%) vs 0, p= 1). There were also no differences in medical (5(10%) vs 3(8%), p=1) or surgical complications (18(35%) vs 9(24%), p=0.35), median (IQR) hospital stay (3.5 (2-5) vs 3.5 (2-4) days, p= 0.44) or 30-day readmissions (4 (8%) vs 2 (5%), p= 1).

Conclusions – In nondiabetic patients undergoing laparoscopic colorectal surgery within an Enhanced Recovery Program, elevated preoperative HbA1c was not associated with increased complications.

Introduction:

Postoperative infections are among the main causes of increased morbidity, length of stay and hospital readmissions (124, 125). These complications place a huge burden on the healthcare system with the costs of surgical site infections alone estimated at more than $3 billion annually in the US (126, 127). Surgical site infections are especially prevalent in colorectal surgery, which is a target for quality improvement in general surgery (128). This has focused attention on preventative strategies.

Perioperative hyperglycemia is strongly associated with postoperative infectious complications (4, 82). This association appears stronger in nondiabetic patients compared to diabetic patients (4, 13). More than one third of people in developed countries have pre-diabetes (129-132), with a reported prevalence as high as 60% in some surgical populations (39-45). Patients with pre-diabetes are at higher risk of developing perioperative hyperglycemia and

insulin resistance (26, 36-38). Identification and optimization of nondiabetic patients at risk for perioperative hyperglycemia is therefore an attractive strategy to improve outcomes.

Traditional screening with random blood sugar, despite being recommended by several practice guidelines (83, 84, 118, 119), is not a reliable test for insulin resistance or dysglycemia because it is highly dependent on the prandial state of the patient (40). Glycosylated hemoglobin (HbA1c) is a type of hemoglobin formed by non-enzymatic glycation of hemoglobin in exposure to plasma glucose (133). HbA1c is a marker of long-term (3-4 month) glucose control and levels between 5.7% and 6.4% are indicative of pre-diabetes in individuals without known diabetes (131). HbA1c is independent of prandial status and is the most specific measure to identify people with pre-diabetes (134). Elevated HbA1c in diabetics is an established indicator of poorer postoperative outcomes and preoperative HbA1c screening is recommended (118, 119). However, the evidence is more limited for nondiabetic patients undergoing abdominal surgery. A systematic review identified only one previous study in colorectal surgery reporting increased odds of overall postoperative complications in nondiabetic patients with elevated HbA1c, but there was no significant increase in infection rates (98, 135).

Prior to wider implementation of preoperative screening with HgA1c in nondiabetic patients, it is necessary to establish its value (136). Hence, the purpose of the current study is to estimate the extent to which elevated preoperative HbA1c is associated with postoperative infectious and overall complications in nondiabetic patients undergoing laparoscopic colorectal resection.

Methods:

This cohort study considered for inclusion 149 consecutive patients undergoing elective laparoscopic colorectal surgery for benign and malignant conditions who were screened for a randomized control trial (RCT) comparing two types of preoperative CHO drinks (identifier: NCT02673502). The study is reported according to the STROBE checklist for cohort studies (www.strobe-statement.org). Data was collected at the Montreal General Hospital site of the McGill University Health Centre between 2016 and 2017. Sixty-one patients were excluded: 30 received plasma glucose modifying interventions such as intraoperative glucose clamp as part of the RCT (n=30), 12 did not have preoperative HbA1c values recorded, 19 were known diabetics. Demographic characteristics, clinical risk factors, operative data and 30-day postoperative outcomes were extracted from medical records. Specifically, we focused on clinical risk factors associated with SSIs, including male gender, BMI, smoking status, American Society of Anesthesiologists' class (ASA), stoma formation, conversion to open surgery, operative time, intra-operative blood loss and receipt of blood transfusion (137, 138). The clinical outcomes of interest were extracted and recorded according to standard definitions as detailed below.

Patients with a previous diagnosis of diabetes were identified and excluded. Nondiabetic patients were classified according to their most recent level of HbA1c within the 3 months prior to the date of surgery, with elevated HbA1c defined as $5.7\% \leq \text{HbA1c} < 6.5$ as per the definition of pre-diabetes according to the American Diabetes Association (ADA)(131).

Setting:

This study was conducted in a university-affiliated tertiary teaching institution. All procedures were performed by one of three colorectal specialists. The perioperative care was according to a dedicated Enhanced Recovery Program (ERP) that includes 23 elements (139); some of these elements were targeted at postoperative surgical site infection (SSIs) prevention

including intravenous antibiotic prophylaxis, no routine abdominal or pelvic drainage and normothermia (5, 139). Of note, a selective mechanical bowel preparation strategy was recommended during this study period, with mechanical bowel prep used routinely for rectal cases but not colon cases, and without oral antibiotics (60). Furthermore, routine perioperative hyperglycemia screening was not included in the ERP.

Outcomes:

The primary outcome was overall infectious complications occurring within 30 days of surgery, defined as the occurrence of at least one of the following: incisional surgical site infections (SSI) (superficial and deep), organ space SSI, urinary tract infection (UTI), pneumonia and/or sepsis as per the National Surgical Quality Improvement Program (NSQIP) definitions (140, 141).

Secondary outcomes included:

1- Overall complications occurring within 30 days of surgery, defined as the patient experiencing at least one complication according to NSQIP definitions (140, 141). These complications were categorized as either surgical, infectious or medical complications (139). The severity of complications was classified according to Clavien-Dindo with severe complications defined as ≥ grade III (100); the 30 day comprehensive complication index (CCI) was calculated for each patient (https://www.assessurgery.com/about_cci-calculator/);

2- Hospital length of stay (LOS), defined as the number of nights the patient spent in the hospital from the day of admission for surgery until discharge. Total LOS was defined as the total number of nights spent in the hospital within 30 days of surgery, including any readmissions related to the surgery within in this period;

3- Readmission rate, defined as a dichotomous variable indicating if the patient was readmitted to the index hospital for care within 30 days of the surgery or not;

4-Preoperative random blood glucose (RBG) levels, defined as the most recent random blood glucose measurement (finger check or laboratory check) within a month prior to the date of surgery;

5- Immediate postoperative RBG level was defined as the first recorded blood glucose measurement in the postoperative care unite (PACU) right after surgery. Postoperative day (POD) 1 RBG level was defined as the highest recorded RBG level on the postoperative day 1. Postoperative RBG level of 7 mmol/l or above was considered mildly elevated and hyperglycemia was defined as RBG≥10mmol/l (13), the recommended level to consider insulin therapy in nondiabetic hospitalized patients (142).

7- Perioperative insulin treatment defined as receipt of insulin at any time during the perioperative period until discharge for primary admission (143).

Data analysis:

Chi square test was used to test categorical data. Independent t-test or Mann-Whitney U test were used to test normally distributed continuous data or not normally distributed continuous data as appropriate.. Preoperative HbA1c level (≥5.7%), age, gender, body mass index (as continuous variable), underlying diagnosis (malignant versus benign), intra operative blood loss (≥300 ml) and operating time (minutes) were included in a multivariate logistic regression analysis; Significance was set at $P < 0.05$. Statistical analysis was conducted using STATA 12 (StataCorp, College Station, TX, USA). Data expressed as mean (SD) unless otherwise specified.

Results:

A total of 88 patients with preoperative HbA1c were identified; when grouped according to preoperative HbA1c levels, 51 patients (48 %) had HbA1c < 5.7% while 37 patients (34 %) had 5.7≤HbA1c<6.5 (pre-diabetes/provisional diabetes) (Figure 1). Demographic and clinical characteristics are summarized in Table 1. Nondiabetic patients with elevated preoperative HbA1c were older compared to nondiabetic patients with normal HbA1c levels (mean age (SD) 54 (16) vs 67 (10), p=0.0001) with no difference in BMI (25(5) vs 27(5) kg/m2, p=0.06) or ASA scores. There were no differences between the two groups with regards to other risk factors for postoperative infections such as malignancy, smoking status, conversion to open surgery, colon versus rectal surgery, stoma formation, intra operative blood loss and transfusions; except for operative (OR) time, which was longer in patients with normal HbA1c levels (median (IQR) 222(167-286) vs 181(129-241) min, p = 0.02).

Association of preoperative HbA1c level with outcomes:

There were no differences between the normal and elevated HbA1c groups in 30-day overall infections (3 (6%) vs 1 (3%), p= 0.63), incisional SSI (2 (4%) vs 1 (3%), p= 1), organ space SSI (1 (2%) vs 0, p= 0.4), UTI (1 (2%) vs 0, p=1), pneumonia (1 (2%) vs 0, p= 1). Overall complications (25 (49%) vs 9 (24%), p= 0.02), severe complications (Clavien III-V) (6 (12%) vs 0, p= 0.03) and CCI (12.5(17) vs 4.8(9.5), p= 0.01) were significantly higher in nondiabetic patients with normal HbA1c levels. There were no differences in median (IQR) hospital stay (3.5 (2-5) vs 3.5 (2-4) days, p= 0.44), total LOS (4(2-6) vs 3.5(2-4.5), p= 0.27) or 30-day readmissions (4 (8%) vs 2 (5%), p= 1) (Table 2).

Association of preoperative HbA1c with pre and postoperative random blood glucose (RBG):

Seventy one patients in total had both preoperative and postoperative RBG levels measured (Table 3). There were no differences between the nondiabetic patients with normal HbA1c and elevated HbA1c in the preoperative RBG (5.4(1) vs 5.5(1) mmol/L, p=0.7), immediate postoperative RBG (7 (2) vs 7.2 (1.5), p= 1) or on POD 1 RBG (6.7(1) vs 6.4(0.6), p= 0.24). There were no differences between nondiabetic patients with normal HbA1c and elevated HbA1c in the proportion of patients experiencing any postoperative RBG ≥10 mmol/L (2(5%) vs 1(3%), p= 1) or ≥7 mmol/L (23(56) vs 18(60), p= 0.8). Only one nondiabetic patient with elevated HbA1c received insulin postoperatively.

Association of perioperative random blood glucose with outcomes:

When nondiabetic patients with recorded postoperative RBG levels (n=71) were grouped according to their post-op RBG, there were no differences in 30-day infections or complications between patients with RBG (>7mmol/l) and patients with normal perioperative blood glucose levels (2 (7%) vs 2 (3%), p= 1 and 17 (56%) vs 17 (41%), p= 0.2).

In multivariate logistic regression, the only independent risk factor for postoperative complications was longer OR time (adjusted OR (95% CI): 1.01(1-1.01)) (Table 4).

Discussion:

Postoperative infections are among the main causes of increased morbidity, length of stay and hospital readmission after surgery (124, 125). Due to the disproportionately high rate of infectious complications after colorectal surgery, attention has been focused on prevention (124, 127, 144). Previous large database studies report an association between perioperative hyperglycemia and surgical site infection in patients undergoing colorectal surgery (4, 145) but few studies investigated the association of preoperative glucose control and outcomes. The aim

of the current study was to evaluate the association of elevated HbA1c (≥5.7%), an indicator of pre-diabetes and dysglycemia, with postoperative infectious complications in nondiabetic patients undergoing scheduled laparoscopic colorectal surgery. However, we found no association between elevated HbA1c and postoperative infections or overall 30-day complications in this population.

The overall rate of infectious complications in the current study was unexpectedly low compared to previous reports of 20% in the colorectal patients in our center(139). This might be due to the fact that emergency cases were excluded, a known risk factor for postoperative infections (145). Furthermore, the cohort included only patients undergoing laparoscopic surgery in an established Enhanced Recovery Pathway, which both contribute to maintenance of insulin sensitivity and reduced infectious complications (50). The findings are consistent with a previous study in colorectal patients that also observed no significant difference in postoperative infections in nondiabetic patients with HbA1c>6 enrolled in an Enhanced Recovery Pathway (98). Unlike the present study, those patients were at higher risk of overall complications. However this was in the context of open surgery and used a higher cut off of 6% to define elevated HBA1c (98) while in the current study cut off of 5.7% was considered for diagnosis of pre-diabetes according to American Diabetes Association guidelines (131). There was an unexpectedly higher rate of overall complications in the nondiabetic patients with normal HbA1c levels. This may have been related to longer operative times in this group, and indeed longer OR time was the only independent risk factor for postoperative complications (adjusted OR (95% CI): 1.01(1-1.01)) (103-106) .

Elevated preoperative HbA1c was not associated with higher perioperative RBG levels in the current cohort of nondiabetic patients, which is inconsistent with previous studies reporting

higher RBG levels in patients with elevated HbA1c levels (113, 146). It has been suggested that even one episode of perioperative hyperglycemia is associated with an increased risk of postoperative complications in nondiabetic colorectal patients (25). However, no difference in the postoperative infectious complications was observed with elevated perioperative RBG in the current population. This might be due to the fact that perioperative RBG levels were not available for all patients within the study and, by nature, RBG is not as consistently informative as fasting blood glucose in reflecting the patient's metabolic status (40).

This study was performed to address the limited evidence investigating HbA1c screening in nondiabetic patients having colorectal surgery, despite the high prevalence of infectious complications in this population. Limitations to the current study may have affected the observed results. The patients in the current study had been screened to participate in a randomized controlled trial, and the results may not be generalizable to other settings. The proportion of consecutive patients screened who were pre-diabetics with elevated HbA1c was quite high (34.5 %), but this is consistent with previous studies where the prevalence of pre-diabetes in patients undergoing non-cardiac surgery who are not known diabetics ranges from 11% to 32% (40, 99, 147). There was missing fasting blood glucose levels in some patients. We only included patients undergoing elective laparoscopic colorectal surgery, and these results may not apply to open colorectal surgery patients or emergency cases.

Conclusions:

In nondiabetic patients, elevated preoperative HbA1c was not associated with higher infectious complications after elective laparoscopic colorectal surgery. Therefore, routine preoperative screening for HbA1c is not recommended in this patient population.

Figure 1 – Patient inclusion/exclusion diagram

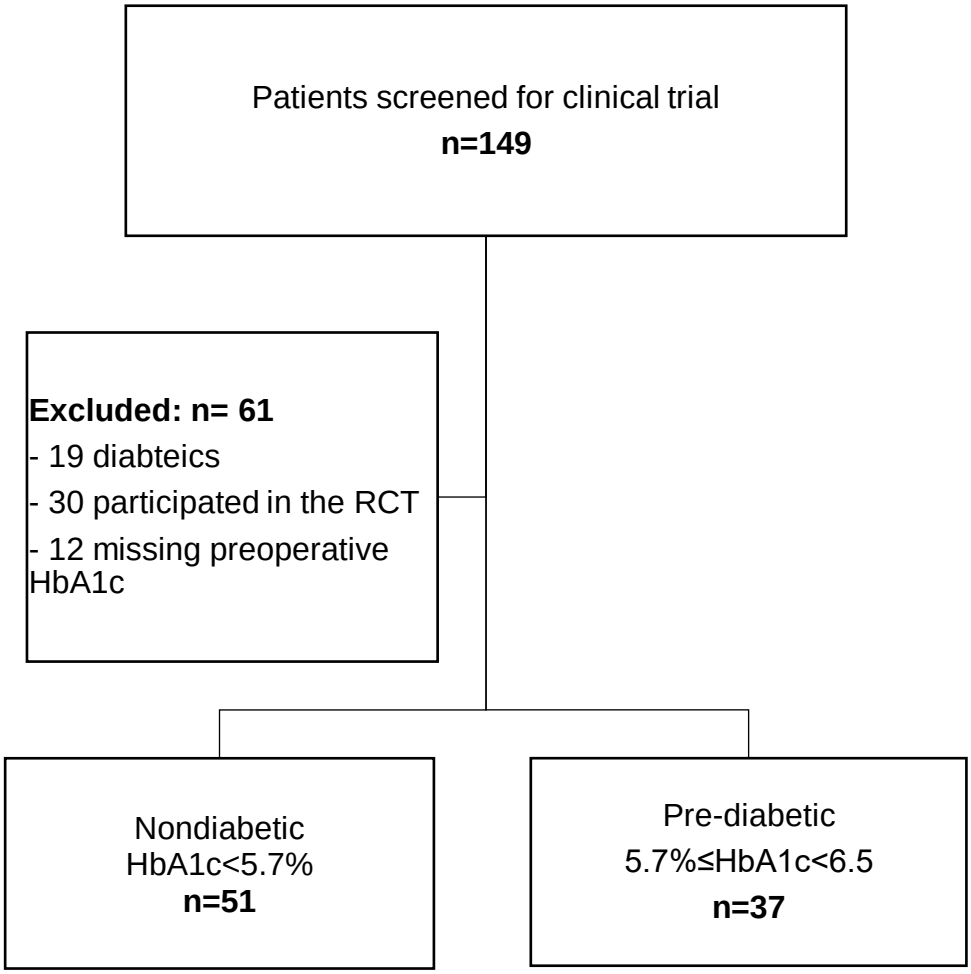

Table 1- Patient demographic and clinical characteristics

Variables	HbA1c<5.7% (n=51)	5.7%≤HbA1c<6.5% (n=37)	P value
Age, mean(SD)	54(16)	67 (10)	<0.01
Female	22(43)	18 (49)	0.66
BMI (Kg/m2), mean(SD)	25 (5)	27 (5)	0.06
ASA			0.34
I-II	35(69)	29(78)	
III- IV	16(31)	8(22)	
Hypertension	17(33)	13(35)	1
Current smoker	9(17)	7(19)	1
Malignancy	28(55)	14(38)	0.13
Surgical approach			
Laparoscopic	45(88)	32(86)	1
Converted to open	6(12)	5(14)	1
Rectal surgery	14 (27)	9(24)	0.80
Stoma formation	12(23)	4(11)	0.16
OR time (minutes), median (IQR)	222 (167-286)	181 (129-241)	0.02
Blood loss (ml), median (IQR)	100(40-250)	100(0-200)	0.43
Intra-operative blood transfusion	1(2)	-	1

Data expressed as number of patients (%) unless specified. P≤0.05 considered significant compared to patients with normal HbA1c (<5.7%) levels.

Table 2- Thirty day postoperative outcomes

Variables	HbA1c<5.7% (n=51)	5.7%≤HbA1c<6.5% (n=37)	P value
Any complication	25(49)	9(24)	0.02
Infectious complications	3(6)	1 (3)	0.63
Any SSI			
Incisional	2(4)	1(3)	1
Organ space	1(2)	0	1
Urinary tract infection	1(2)	0	1
Pneumonia	1(2)	0	1
Surgical complications	18(35)	9(24)	0.35
Anastomotic leak	1(2)	0	1
Ileus	11(21)	2(5)	0.06
Other surgical complications*	6(12)	7(19)	0.37
Medical complications	5(10)	3(8)	1
Respiratory complications	0	1(3)	0.42
Cardiac complications	3(6)	2(5)	1
Deep vein thrombosis	1(2)	2(5)	0.57
Acute renal insufficiency	2(4)	1(3)	1
Complication severity (highest Clavien)			
Clavien I-II	19(37)	9(24)	0.24
Clavien III-IV	6(12)	0	0.03
Comprehensive complication index (CCI)	12.5(17)	4.8(9.5)	0.01
Death	0	0	
Primary length of stay (days), median (IQR)	3.5(2-5)	3.5(2-4)	0.44
Readmissions	4(8)	2(5)	1
Total length of stay (days), median (IQR)	4(2-6)	3.5(2-4.5)	0.27

Data expressed as number of patients (%) unless specified. SSI= surgical site infection. P≤0.05 considered significant compared to patients with normal HbA1c (<5.7%) levels.
* Other surgical complications such as bleeding, mechanical bowel obstruction, bowel perforation and wound dehiscence.

Table 3- Perioperative random blood glucose levels (mmol/L), mean (SD)

Variables	HbA1c<5.7% (n=41)	5.7%≤HbA1c<6.5% (n=30)	P value
Preoperative	5.4 (1)	5.5(1)	0.7
Immediate post-op	7 (2)	7. 2(1.5)	1
Postoperative Day 1	6.7(1)	6.4(0.6)	0.24

Only patients who had RBG levels recorded for all three time points were included in the analysis. RBG = random blood glucose.

Table 4- Multivariate model for risk of postoperative complications

Variables	Univariate analysis			Multivariate analysis		
	Odds ratio	**95% CI**	**P-Value**	**Odds ratio**	**95% CI**	**P-value**
HbA1c≥5.7%	0.33	0.13 - 0.85	0.02	0.46	0.15 - 1.44	0.18
Age	0.99	0.96 - 1.02	0.48	1.02	0.98 - 1.06	0.28
BMI (kg/m^2)	0.99	0.91 - 1.08	0.8	0.97	0.88 - 1.07	0.57
Female	0.62	0.26- 1.48	0.28	0.55	0.2- 1.50	0.24
Malignancy	0.63	0.26 – 1.53	0.31	0.42	0.13 - 1.33	0.14
Rectal surgery	0.79	0.42 – 1.48	0.46	1.13	0.51 - 2.51	0.75
Blood loss ≥300 ml	2.07	0.67 - 6.34	0.2	1.01	0.26 - 3.95	0.98
OR time (minutes)	1.01	1 - 1.01	0.01	1.01	1 - 1.01	0.01

Univariate and multivariate model for risk of 30day postoperative complications. Number of patients = 88

CHAPTER 3: PREVENTING AND REDUCING PERIOPERATIVE INSULIN RESISTANCE

3.1 Preamble:

The prospective cohort study in the previous chapter indicated that there was no relationship between elevated preoperative HbA1c levels and postoperative outcomes in nondiabetic patients undergoing elective laparoscopic colorectal surgeries. Patients with elevated preoperative HbA1c did not even have an increased risk of hyperglycemia on POD1, regardless of cutoff (ie. RBG >7mmol/L or RBG >10 mmol/L). It is possible that the reason for this observation is that insulin sensitivity might be maintained in the context of colorectal surgeries done laparoscopically within an ERP. If so, will this impact the value of other interventions recommended to modulate the stress response, such as CHO loading?

Preoperative CHO loading by provision of drinks containing complex carbohydrates i.e. maltodextrin are recommended based on studies in open surgery where there was a significant stress response (24, 61-64); however they are cumbersome for patients and have a cost. Whether CHO drinks containing simple CHO can be used instead in the context of modern surgery with maintained insulin sensitivity is unknown.

We studied the provision of simple CHO drinks in two ways: first, whether insulin response to simple CHO can be "boosted" by adding whey protein: and 2nd, whether simple CHO alone were as effective as complex CHO.

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3.2 The effects of added whey protein to a preoperative carbohydrate drink on glucose and insulin response

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Abstract:

Background: Preoperative complex carbohydrate (CHO) drinks are recommended to attenuate postoperative insulin resistance. However, many institutions use simple CHO drinks, which while convenient, may have less metabolic effects. Whey protein may enhance insulin release when added to complex CHO. The aim of this study was to compare the insulin response to simple CHO versus simple CHO supplemented with whey protein.

Methods: Twelve healthy volunteers participated in this double-blinded, within subject, cross-over design study investigating insulin response to simple CHO drink versus simple CHO+ whey (CHO+W) drink. The primary outcome was the accumulated insulin response during 180 minutes after ingestion of the drinks (Area under the curve, AUC). Secondary outcomes included plasma glucose and ghrelin levels, and gastric emptying rate estimated by acetaminophen absorption technique. Data presented as mean (SD).

Results: There was no differences in accumulated insulin response after the CHO or CHO+W drinks (AUC: 15(8) vs 20(14) nmol/l, p=0.27). Insulin and glucose levels peaked between 30 and 60 minutes and reached 215(95) pmol/l and 7(1) mmol/l after the CHO drink and to 264(232) pmol/l and 6.5(1) mmol/l after the CHO+W drink. There were no differences in glucose or ghrelin levels or gastric emptying with the addition of whey.

Conclusion: The addition of whey protein to a simple CHO drink did not change the insulin response in healthy individuals. The peak insulin responses to simple CHO with or without whey protein were lower than that previously reported with complex CHO drinks. The impact of simple carbohydrate drinks with lower insulin response on perioperative insulin sensitivity requires further study.

Introduction:

Provision of a clear carbohydrate (CHO)-rich beverage 2 h before surgery is recommended in guidelines as a component of optimal perioperative care within a multimodal Enhanced Recovery after Surgery (ERAS) pathway (60). The rationale for administering a CHO drink is to prepare the patient for surgery by maximizing energy (glycogen) stores and preserving the liver and peripheral tissue sensitivity to insulin**;** in other words, preoperative CHO drink creates a ”fed” state in which the patient is better able to withstand the impending surgical catabolic response and to utilize the nutrients provided (148).

In previous studies, CHO drinks were reported to attenuate preoperative feelings of thirst, hunger and anxiety (67), reduce postoperative insulin resistance (61) and decrease loss of muscle mass (64). The CHO drink used in these studies was most commonly a 400 ml clear beverage containing 50g of the complex carbohydrate maltodextrin in order to minimize the osmotic load compared to simple carbohydrate containing drinks (6, 7, 9, 10). Maltodextrin is polysaccharide consisting of multiple chains of D-glucose units. This formulation has only recently become commercially available in North America, and several leading institutions with well-developed ERAS programs report the use of readily available simple carbohydrate drinks instead (149). However it is unclear whether these drinks provide the degree of insulin response required for the metabolic impact seen with complex carbohydrate drinks (67). The addition of whey protein to complex CHO drinks containing maltodextrin has been shown to be effective in reducing surgically- induced insulin resistance as well as contributing to the preoperative fed state (74, 75). Whey is a water soluble protein from milk which is an abundant source of branched-chain amino acids (BCAAs) such as leucine, isoleucine and valine; the essential BCCAAs have synergistic insulinotropic effects when added to carbohydrates (76, 77). Furthermore, whey has

been shown to be an effective satiating proteins; this is evident by its suppressing effect on ghrelin levels in blood (78).Ghrelin is a peptide secreted from gastrointestinal tract; its levels surge with hunger and decline with food ingestion (150).

The addition of whey may therefore be an attractive strategy to augment the amplitude of the insulin response induced by the preoperative provision of drinks containing simple CHO for centers in which complex CHO drinks are not available. However, previous systematic reviews and meta-analysis on preoperative CHO +/- protein drinks provide limited evidence with regards to the insulin response triggered by simple CHO alone or with additional protein drinks (72, 73). The purpose of this study was therefore to compare the metabolic response to a simple CHO drink versus a simple CHO drink with whey protein in healthy individuals. We hypothesized that the addition of whey protein would enhance the accumulated insulin and ghrelin response to a simple CHO drink.

Methods:

Subjects:

This double-blinded, within subject, cross-over design study was approved by the McGill University Health Center (MUHC) Research Ethics Board (13-168-BMA) and all participants signed a written informed consent. The trial was registered at www.ClinicalTrials.gov (NCT01971229).

Healthy volunteers over 40 years of age were recruited through advertisements in local newspapers and on the internal MUHC webpage. The age range was chosen to approximate the population undergoing elective colorectal surgery. The following exclusion criteria were applied: diabetes, neurological disorders, chronic kidney failure, chronic liver disease, gastroesophageal

reflux, achalasia, gastroparesis or intestinal obstruction, previous abdominal surgery, lactose intolerance, and allergy to acetaminophen.

Outcomes:

The primary outcome was the accumulative insulin response induced by simple CHO drink (pulpless orange juice) versus simple CHO+W drink as indicated by the area under the curve (AUC) of insulin secretion during 180 minutes.

Secondary outcomes included:

1- Plasma levels of insulin, glucose and ghrelin at various time points up to 180 minutes after ingestion of the drinks

2- The gastric half-emptying time (T50) for the two drinks, as by the acetaminophen absorption technique.

Experimental protocol:

Each volunteer received the drinks on two separate sessions, one week apart, to allow for any possible residual effect of the first drink to fade; the session orders were randomized. Participants were instructed not to consume alcohol the day prior to each testing session, to abstain from caffeine-containing beverages during each testing day and to abstain from solid food and any drink other than water after midnight. Testing sessions were performed in a fully equipped clinical room in the Department of Anesthesia at the Montreal General Hospital during morning hours.

Volunteers arrived at 7:30 am and following a 30 min rest, a venous cannula was inserted in the antecubital fossa for blood sampling. Participants remained in a semi-reclined position for the entire study. They then received the drink to be consumed within 10 minutes. All volunteers

were assigned in a randomized fashion to drink either 400 ml of simple CHO drink (no pulp orange juice, Minute Maid, 50 g CHO; 648 mOsmol/L; pH 3.7; 180 kcal) or 400 ml of the simple CHO+ Whey preparation; this preparation contained the same clear orange juice to which whey protein (lactalbumin) was added (50 g CHO; whey protein 12.2 g; water 63 ml; 650 mOsm/L; pH 3.3; 224 kcal). The amount of added whey protein was determined to be sufficient to cover the protein requirement of a small meal (<15 gr). The drinks were prepared in identical non-transparent containers and were provided to the investigator by the research coordinator responsible for randomization. Both investigators and volunteers were blinded from the type of drink administered. Blood samples were taken at time 0 (before the drink) and 15, 30, 60, 90, 120, 150 and 180 min after the ingestion of the drink. Subjects completed the standard 100mm visual analogue scale (VAS) to indicate their level of nausea, thirst, hunger, tiredness and weakness after ingestion of the drinks.

Measurement of glucose, insulin and ghrelin:

Blood samples were taken at each time point in appropriate tubes (BD Vacutainer™) and were kept on ice. Following centrifugation at 2000 x g at 4°C, the plasma was separated and kept in -80 °C freezer for later analysis. Plasma glucose was measured enzymatically using a glucose analyzer 2 (Beckman Instruments, Fullerton, CA, USA). Insulin levels were measured by radioimmunoassay (Amersham International, Amersham, Bucks, UK). Plasma concentrations of ghrelin were assayed by ELISA (MesoScale Diagnostics, Rockville, MD, USA).

Estimation of gastric emptying:

We employed the acetaminophen absorption test to compare estimated gastric emptying after ingestion of the drinks. Since orally administered acetaminophen is not well absorbed in the

stomach but is rapidly absorbed in the small intestine, the rate of appearance in the blood reflects the rate of gastric emptying (14). The technique has been found to correlate well to scintigraphy under standardized conditions such as in the current study (151, 152). A dose of 1.5 g of acetaminophen was dissolved in 100 mL water and was given together with the drinks**.** Plasma acetaminophen was measured by the AxSYM acetaminophen assay (Abbott Laboratories, Chicago, IL, USA). According to a previously described method (153), the gastric emptying profile was modelled after conversion of plasma acetaminophen concentration values to cumulated values, assuming total absorption of the drug during 180 min after the meal. Hence, the inverted cumulated absorption curve was used to estimate the emptying profile of the drug from the stomach. The gastric half-emptying time (T50) was calculated as the time when 50% of the total cumulated acetaminophen dose had been emptied. The amount of contents retained at 120 min was also calculated as this time point is often used as a cut off for slow gastric emptying.

Sample size estimate and statistical analysis:

The primary endpoint of interest was the accumulated serum insulin release measured as the area under the curve of insulin secretion over 180 min (AUC 180). Based on a similar study where a glucose only drink was compared to a glucose drink enriched with amino acids (77), a sample size of 12 volunteers per group was calculated for the current cross-over study design based on a power of 80% ($\beta = 0.2$), SD of 28 nmol-3h/L and a significance level of 95% ($\alpha = 0.05$) to detect a difference of 35 nmol-3h/L. Values for plasma glucose and serum insulin and plasma ghrelin are presented as mean (SD). Statistical analysis was performed with STATA 12 (StataCorp, College Station, TX, USA). Data were compared using paired student T-test or ANOVA with Tukey's multiple comparisons test as appropriate.

Results:

Twelve healthy volunteers with mean (SD) age 54.2 (10) years, body weight 78.3 (10.4) kg; and body mass index (BMI) 25.1 (2.8) kg/m^2were recruited. Both drinks were well tolerated by all volunteers. There were no differences between the two groups in the scales of nausea, thirst, hunger, tiredness and weakness. Drinks were finished within the allotted time.

Plasma Glucose and Serum insulin and Plasma Ghrelin:

There were no differences in insulin, glucose or ghrelin levels at baseline for the two drinks (Table 1). Both drinks resulted in a significant increase in both plasma glucose and serum insulin concentrations compared to baseline ($p < 0.05$) with a peak between 30 and 60 min following ingestion of both drinks. Insulin reached peak values of 215(95) pmol/l [median (IQR) 198 (177.5-214.5)] after the CHO drink and 264(232) pmol/l [median (IQR) 251(150-282)] after the CHO+W drink. Glucose reached peak concentration of 7(1) mmol/l after the CHO drink and 6.5(1) mmol/l after the CHO+W drink. No differences were found in accumulated serum insulin over 180 minutes [AUC180: 15 (8.0) vs 20.26(13.65) nmol/l p=0.27] or accumulated glucose [AUC180: 0.98 (0.11) vs 1(0.1) mol/l p=0.59] after the two drinks (Figure2 a, b).

Plasma ghrelin declined similarly after both the CHO and CHO+W drinks with respective nadirs of 22.6(17) ng/l and 19.4(16.3) ng/l at 90 min after intake. Thereafter the ghrelin levels increased in concordance with gastric emptying (Figure 2c). However, no differences were found in accumulated ghrelin levels over 180 minutes after CHO or CHO+W [265.6(236.5) vs 225.4(226.5) ng/l, p=0.67].

Gastric emptying:

There were no significant differences in estimated gastric emptying rate of the CHO or CHO+W drink (T50 76.3 (5.6) min vs 80.2 (3.8) min), p=0.07). Estimated gastric retention at 120 min was 21 (2.8) % after the CHO drink versus 21.6 (1.9) % after the CHO+ W drink, p=0.54 (Figure 3).

Discussion:

We compared the insulin response triggered by ingestion of a simple CHO drink alone versus when whey protein was added to it in healthy individuals. Ingestion of a simple CHO drink (simple orange juice) with or without whey protein was followed by a significant release of serum insulin within the first 60 min and a drop in ghrelin. Addition of whey protein to the simple CHO drink had no impact on the accumulated insulin response provoked by the drinks. In addition, full gastric emptying of these two drinks was achieved at around 180 min post ingestion. There were no side effects reported with either drink.

The rationale for the use of CHO drink before surgery is based on the understanding that prolonged fasting before surgery induces a catabolic state (154). The functional purpose of the CHO load is therefore meant to be two-fold: 1) to allow maximal glycogen storage and a metabolically fed state at the start of surgery; 2) to preserve insulin's anabolic action. Ingestion of a CHO drink mimics that of a meal and evokes an insulin response which counteracts the effect of catabolic hormones, such as growth hormone, epinephrine and cortisol, on the hepatic production of gluconeogenic substrates, thus increasing insulin sensitivity (148).

There is sufficient evidence that a preoperative complex CHO drink increases insulin sensitivity before surgery and attenuates the establishment of insulin resistance in the postoperative period (61). Furthermore, postoperative insulin resistance was decreased by half

when whey protein was added to a complex CHO drink pre- operatively compared to water alone (75). The effect on postoperative insulin resistance exerted by the CHO drink might result from the physiological hyperinsulinemia and not from the glucose load itself (20). Addition of proteins such as whey containing insulinotropic amino acids might contribute to the physiologic hyperinsulinemia (155).

The serum concentration of insulin increased after the ingestion of both drinks reaching a peak between 30 and 60 min, however, there was no significant difference between the accumulated insulin responses to the two drinks at 180 minutes. The peak concentration of insulin after either drink was 215-264 pmol/l (30-38 µIU/mL) in the current study. This is considerably lower than the insulin levels reported by Nygren (67) in similar time points (451 pmol/l or 65 µIU/ml) where patients ingested complex CHO drinks which contained maltodextrin. In contrast, our CHO drink contained 50% disaccharide sucrose, a combination of the monosaccharides glucose and fructose. Therefore the higher release of serum insulin following the ingestion of the same amount of CHO can be explained by the greater insulin response provoked by complex CHOs**.** Addition of whey protein to a simple CHO drink in the current study does not seem to compensate for the lower insulin response to simple CHO we observed compared to the previously reported complex CHO drinks. However, this finding does not necessarily imply an inability to enhance peripheral tissue insulin sensitivity; in fact there are some preliminary findings suggesting that administration of a 2.5% carbohydrate mixture of mono- and disaccharides to volunteers was sufficient to increase insulin sensitivity as measured with the gold-standard hyperinsulinemic normoglycemic clamp (156).

Plasma ghrelin concentration varies throughout the day. Peak levels are found under fasting conditions before meals, and at night; ghrelin levels in plasma fall within 60 min of a

meal (157), particularly following meals rich in carbohydrate content (158-160). Ghrelin also counterbalances insulin after food intake in order to regulate and offset insulin effects after ingestion (157). Taken together, balanced nutritional intake comprises both insulin and ghrelin excursions in blood. Appropriate ghrelin suppression is therefore likely to prolong satiety (161). This pattern was seen to a similar extent with both the CHO and CHO+W drinks and is consistent with the finding that CHO drinks reduce the feeling of preoperative hunger (67).

The gastric emptying rates of the CHO drinks with or without whey protein were similar (T50: 80 and 76 mins). However, these rates were somewhat slower than previously studied maltodextrin containing drinks (less than 60 mins)(151, 162, 163). As multiple factors such as volume, pH, caloric intake and composition of fluids can affect gastric emptying (164), it is possible that the lower pH of (3.3 versus 6.9) as well as the type of CHO content (simple versus complex) of the current study drinks are responsible for their slower gastric emtying compared to drinks containing complex CHO (151, 162, 163). There are also limitations to the use of plasma acethaminophen levels to estimate the post meal gastric emptying. The gastric emptying estimation with this techinique is dependent on the pharmokinetics of acetaminophen which is variable within and between individuals (165). However, still the results of this test correlates well with the gold standard scintigraphy(152) . Nevertheless, we should interpret the current study's gastric emptying time results with caution, but whey did not further delay gastric emptying compared to CHO alone. With regard to evaluating the safety of simple CHO drinks +/- whey provision in the preoperative period, more precise methods should be used to evaluate their gastric emptying properties.

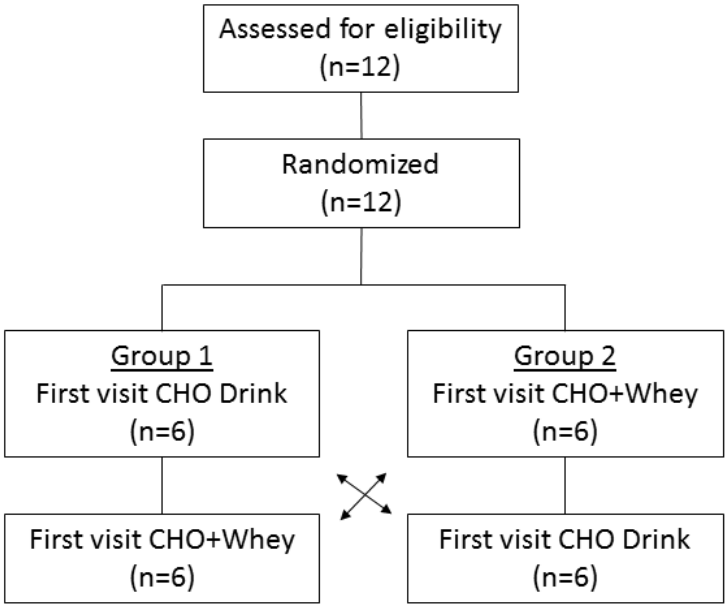
In addition to the estimation of gastric emptying, there are other limitations to the study. A third group including a complex CHO drink would have been informative, however the

preoperative drink was not commercially available in Canada at the time of the study. In the absence of this drink, we evalauted whether an augmented insulin response could be achieved with the addition of whey protein. The use of commercial orange juice was a pragmatic choice as it is being used clinically, however the presence of fructose may decreased the dose of insulin-stimulating carbohydrate. The sample size was small, with significant variability between the groups at individual time points. However, the primary outcome of the study, the accumulated insulin response, was not different between the groups. In addition, the cross-over design of the study reduces the risk for type two error by reducing between-individual variability.

Although the cross-over design of the study reduced sample size requirements by reducing between-individual variability, there was significant between groups variability at individual time points due to the presence of outliers; therefore, we cannot exclude that our findings are subject to type II error.

In conclusion, the amplitude of the insulin response to simple CHO drink was not augmented with the addition of whey protein in healthy individuals. However, the peak insulin response for both drinks seemed to be considerably lower than previously studied complex CHO drinks which are recommended in perioperative care guidelines. Whether this impacts insulin sensitivity in the perioperative setting requires additional study.

Figure1- Study design



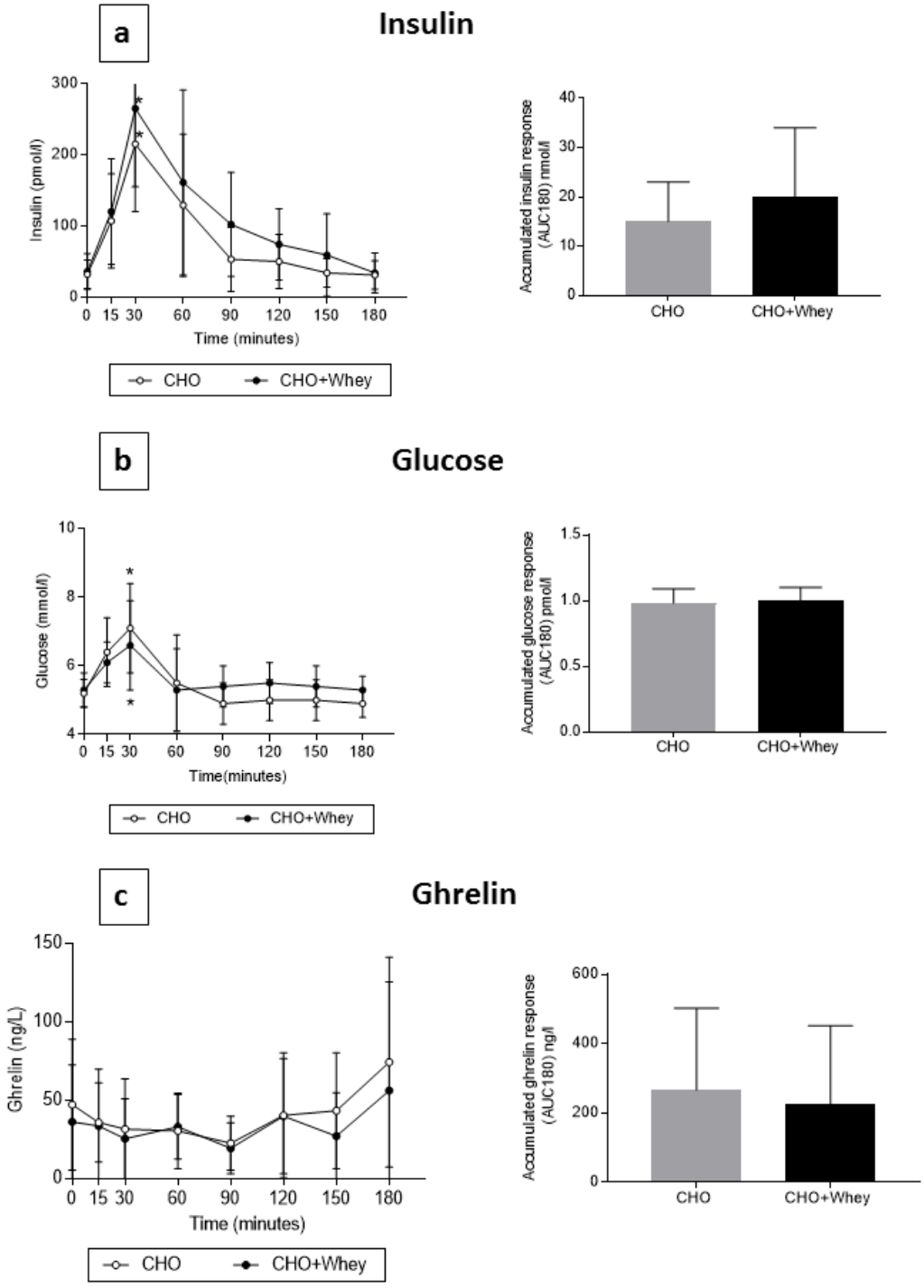


Figure 2- Left panels- Changes in plasma insulin (A), glucose (B) and ghrelin (C) concentrations over 180 min after having the drinks; *P < 0.05 vs. baseline B- Right panels- Accumulated insulin, glucose and ghrelin responses calculated as the area under the curve of glucose secretion in 180 min (AUC180). Data are presented as Mean (SD).

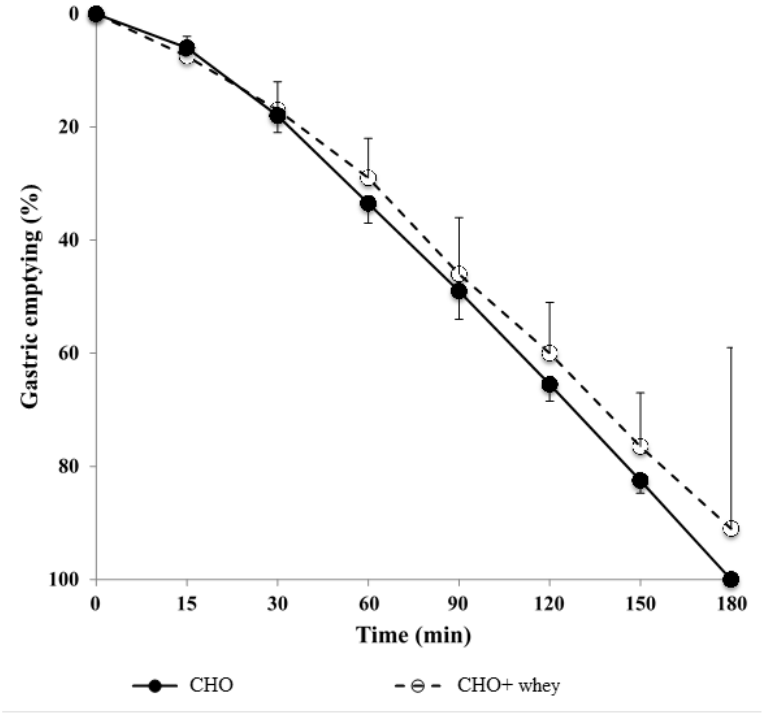


Figure3- Estimation of gastric emptying after ingestion of CHO drink compared to CHO + whey drink.

Time (minutes)	Insulin (pmol/l) mean (SD)			Glucose (mmol/l) mean (SD)			Ghrelin (ng/l) mean (SD)		
	CHO	**CHO+ W**	**P value**	**CHO**	**CHO+ W**	**P value**	**CHO**	**CHO+ W**	**P value**
T0	32(20)	36(25)	0.6	5.2(0.4)	5.3(0.5)	0.5	47.3(41.8)	36.3(36.4)	0.49
T15	107(66)	120(74)	0.65	6.4(1)	6.1(0.6)	0.3	35.9(25.2)	33.7(36.4)	0.86
T30	215(95)	265(233)	0.49	7.1(1.3)	6.6(1.3)	0.35	31.6(32.3	25.5(25.6)	0.61
T60	129(126)	161(153)	0.58	5.5(1.4)	5.3(1.2)	0.7	30.5(24)	30.6(21.5)	0.99
T90	53(45)	102(73)	0.06	4.9(0.6)	5.4(0.6)	0.055	22.6(17)	19.4(16.3)	0.64
T120	50(38)	74(50)	0.1	5(0.6)	5.5(0.7)	0.07	40.4(39.9)	39.9(36.7)	0.97
T150	34(20)	59(50)	0.12	5(0.6)	5.4(0.6)	0.11	43.4(37)	25(29.1)	0.18
T180	31(20)	34(28)	0.7	4.9(0.5)	5.3(0.5)	0.06	68.6(70)	56.3(69.6)	0.67

Table 1- Plasma insulin, glucose and ghrelin levels

Plasma insulin, glucose and ghrelin levels at different time points compared between CHO group and CHO+ whey (CHO+W) Group. Data are presented as mean (SD).

3.3 Preamble:

The previous study on the impact of addition of whey protein on the insulin response triggered by simple CHO drinks indicated that the insulin response to simple CHO drinks was much lower than that previously reported for complex CHO drinks. The addition of whey protein, despite its insulinotropic properties, could not enhance this response in healthy volunteers.

However, it is unclear whether this lower insulin response would negate the ability of simple CHO drinks to preserve perioperative insulin sensitivity, compared to what is seen with complex CHO drinks. Therefore, the impact of simple CHO drinks with lower insulin response on perioperative insulin sensitivity requires further study. Accordingly, we performed a randomized control trial comparing intraoperative and postoperative insulin sensitivity after simple or complex CHO drinks in patients undergoing elective laparoscopic colon resection.

The manuscript for this study is accepted for publication at Annals of Surgery (IF=9.2).

3.4 Simple versus Complex preoperative carbohydrate drink to preserve perioperative insulin sensitivity in laparoscopic colectomy: A randomized controlled trial

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Abstract:

Introduction: Administration of a preoperative drink containing complex carbohydrate (CHO) preserves insulin sensitivity after traditional colorectal surgery compared to water or fasting, however its benefits compared to simple CHO drinks have not been investigated. This randomised controlled trial estimated the extent to which a preoperative simple CHO drink preserves insulin sensitivity, compared to a complex CHO drink.

Methods: This randomized trial involved 30 nondiabetic adult patients undergoing laparoscopic colon resection. Perioperative care followed an established Enhanced Recovery Pathway (ERP). Patients were randomized 1:1 to receive either a simple CHO drink (400 ml containing 50gr of fructose) or a complex CHO drink (400ml containing 40gr of maltodextrin and 10gr of fructose) 2 hours before surgery. The primary outcome was intraoperative insulin sensitivity assessed by peripheral glucose uptake (M value) during hyperinsulinemic euglycemic clamp. Secondary outcomes included postoperative hepatic insulin resistance assessed by Homeostatic model assessment (HOMA2-IR), fasting blood glucose (FBG) and C-reactive protein (CRP) at baseline and postoperative day (POD 1-3), 30-day complications and hospital length of stay (LOS).

Results: Intraoperative insulin sensitivity was maintained in both groups with no difference following ingestion of the simple or complex CHO drink (mean (SD) M value 8.3(3.3) vs 8.8(3.8) mg/kg/min, p=0.7). Postoperative insulin sensitivity was maintained, with no differences in hepatic insulin resistance (HOMA2-IR) or fasting blood glucose on POD 1-3. There were no differences in complications or LOS.

Conclusions: After laparoscopic colectomy in an ERP, perioperative insulin sensitivity was maintained and not further impacted by the preoperative ingestion of a complex or simple CHO drink.

Introduction:

Major surgery triggers a metabolic stress response that results in a transient state of insulin resistance caused by increased production of glucose, decreased peripheral uptake of glucose and reduced glycogen synthesis ("diabetes of surgery")(18, 166). The degree of insulin resistance is highest on the day after surgery and may last for several weeks (18). Multiple factors contribute to the magnitude of the response, including the degree of invasiveness of the procedure, anesthesia and analgesia techniques, blood loss, duration of the surgery, nutrition and physical activity (18). Reduced insulin sensitivity is the main driver disrupting glucose/protein metabolic hemostasis after surgery and is linked to postoperative hyperglycemia, complications, infections and longer length of stay (8). Patients with insulin resistance at baseline experience a greater extent of protein loss after abdominal surgery (167) which is associated with reduced immune function, delayed wound healing and decreased muscle strength postoperative (8). Even a single episode of hyperglycemia postoperative is linked to elevated morbidity and mortality in nondiabetic patients after colorectal surgery (25).

Enhanced Recovery Pathways (ERPs) include multiple anticatabolic interventions delivered throughout the perioperative period that aim to attenuate the surgical stress response, support rapid physiologic and functional recovery and reduce morbidity (55, 56). These include

minimally invasive surgery, early nutrition and mobilization. Provision of a carbohydrate drink (CHO) containing 50 grams of complex carbohydrate 2 hours before surgery has been proposed as a strategy to alter the metabolic condition of the patient entering surgery from the fasting to the fed state by stimulating insulin release, similar to what is seen after a meal. There is evidence that CHO loading before surgery reduces postoperative insulin resistance (24, 61-63), preserves postoperative muscle mass (64) and improves patient' wellbeing, thirst and hunger (67, 68), without affecting complications (72, 168, 169). Preoperative CHO is recommended in guidelines from the Enhanced Recovery after Surgery (ERAS) Society, the American Society of Colon and Rectal Surgeons (ASCRS) and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) to improve recovery after colorectal surgery (59, 60). However, the evidence pertaining to the benefit of CHO drinks on attenuating surgical induced insulin resistance is confined to mostly drinks containing complex carbohydrate compared to fasting or placebo.

In practice, several ERPs use commercially available fruit juices (69) or sports drinks (eg Gatorade™) for preoperative CHO loading (4, 70). While fruit juices and sports drinks are easily accessible and inexpensive, the carbohydrate content of these drinks is different from that shown to attenuate insulin resistance in previous studies, which contained 70% complex carbohydrate (i.e. maltodextrin) to minimize the osmotic load (61-63, 148). In contrast, fruit juices and sports drinks contain simple carbohydrates such as fructose and glucose. There are considerable differences in absorption and metabolism of complex and simple carbohydrates in the body as well as the magnitude of the insulin response they trigger (69). Fructose has a very low glycemic index (i.e. a ranking of how quickly the body metabolises 50 grams of a particular carbohydrate on a scale of 0-100) (71) of 19 ± 2 while maltodextrin has a glycemic index ranging from 85 to 105. Therefore, the insulin response induced by ingestion of a simple CHO drink may be

significantly lower than after ingestion of a drink containing maltodextrin (69). Whether this lower insulin response will eliminate the benefit on insulin sensitivity is not known, especially when used in addition with other ERP interventions aimed at reducing surgical stress, such as laparoscopic surgery, avoidance of fasting and early nutrition and mobilization.

The aim of this randomised controlled trial was to estimate the extent to which ingestion of a preoperative simple CHO drink impacts perioperative insulin resistance in patients undergoing laparoscopic colectomy surgery in an ERP, compared to a drink containing complex CHO.

Methods:

Study design and patients:

The current prospective, double-blinded randomized controlled trial was approved by the McGill University Health Center (15-162-MUHC) and registered on ClinicalTrials.gov (Identifier: NCT02673502). Trial reporting is according to the Consort checklist (www.consort-statement.org). Nondiabetic patients scheduled for elective laparoscopic colon resection without a stoma, who were older than 18 years, had HbA1c $\leq$ 5.7% and were not receiving any glucose lowering medications were considered for enrolment; patients were excluded from the study if they were diagnosed with diabetes or pre-diabetes according to the criteria listed in Appendix1. Routine standard preoperative and postoperative care followed ERAS Society guidelines using an ERP established in 2010 (139, 170). The ERP includes written educational material for patients and standard orders specifying multimodal analgesia, balanced fluids, early nutrition, early mobilization, avoidance of drains and a target discharge of 3 days (21, 22). Patients did not

receive dexamethasone (known to increase insulin resistance (171)) and postoperative pain control was achieved through patient-controlled analgesia (PCA) with morphine.

Randomization and blinding:

The patients were randomized on the day of surgery to either receive the simple CHO drink or the complex CHO drink using a computerized program. The patients, the surgeons and the researchers performing the study procedures and assessments were all blinded to the randomization order. To ensure blinding, the drinks were prepared in identical opaque containers with the same shape and appearance.

Interventions:

Patients were instructed to ingest 400 ml of the CHO drink within a 10-minute time span, 2 hours before surgery, under observation of a member of the research team who was blinded to randomization. The simple CHO drink consisted of 400 ml of commercial orange juice (Minute Maid® Without Pulp) containing 50 grams of fructose/galactose (648 mOsm/kg, PH 3.7). The complex CHO drink contained 40 grams of complex carbohydrate (maltodextrin) and 10 grams simple carbohydrate (207 mOsm/kg, PH 4.5) and was made by dissolving maltodextrin powder (Bulk Powders®) in water and adding a calculated volume of orange juice to achieve the same color and flavour.

Outcome measures:

Intraoperative insulin sensitivity-The primary outcome was intraoperative insulin sensitivity measured using the hyperinsulinemic euglycemic glucose clamp (HEC), the "gold standard" technique (172, 173). The technique involves the administration of a constant dose of insulin with simultaneous glucose infusion at variable rates; the lower the glucose infusion rate

(GIR) necessary to maintain euglycemia the greater the degree of insulin resistance (172, 173). In this method, constant infusion of exogenous insulin at levels enough to suppress hepatic glucose production results in the development of a new steady state, in which exogenous glucose infusion at a rate sufficient to maintain euglycemia equals the amount of glucose disposal in the muscle and adipose tissue (M value) (174). Glucose uptake by skeletal muscle, is thought to be the main cause of perioperative insulin resistance (172, 173). Using an IV cannula, a primed infusion of regular insulin was started and maintained at a rate of 2.5 mU/Kg $_{FFM}$ /min together with various infusion rates of Dextrose 10% to maintain a blood glucose level at 5.5 mmol/l. Blood sampling was done through an arterial line inserted routinely for colectomy. Arterial blood glucose was measured every 10 minutes using a glucometer (Accu-Check®). Time to reach to euglycemia was recorded. The M value (mg/kg/min), representing the mean glucose infusion rate required to maintain normoglycemia during HEC, was calculated after a plateau duration of at least 30 minutes. In order to account for the very small amount of glucose disposal in the adipose tissue and to avoid over estimation of insulin resistance in patients with higher BMI, M values were normalized to lean fat-free body mass (FFM) (174). M values below 5.5 mg/kg/min represent a state of insulin resistance (37).

Postoperative insulin resistance- To reduce the burden on patients, HEC was limited to the intraoperative phase. Instead, the homeostatic model assessment (HOMA2 computerized model) method was used to estimate baseline (before surgery) and postoperative (POD 1-3) insulin resistance (HOMA2-IR), insulin sensitivity (HOMA2-%S) and beta cell function (HOMA2-%B)(https://www.dtu.ox.ac.uk/ToolsSoftware/). In the fasting condition, insulin regulates the level of glycemia by controlling hepatic glucose production which equals whole

body glucose disposal. HOMA2 represents the balance between hepatic glucose output and insulin secretion and represents hepatic insulin resistance (174).

For the purpose of calculating HOMA2, fasting plasma glucose (FBG) and insulin were measured from blood samples collected preoperative and every morning on POD 1 through 3. Previously reported HOMA-IR levels in healthy nondiabetic populations were used to define insulin resistance (ie 2.06 in men and 1.95 in women) (175, 176).

Residual gastric volume-An orogastric tube was inserted immediately following induction of anesthesia in order to measure the amount of residual liquid in the stomach.

Other outcomes- Serum C-reactive protein (CRP) levels were measured to assess inflammation on the mornings of POD1-3. Grip strength, a marker of overall physical recovery, was measured by a hand grip dynamometer at baseline in the preoperative clinic and 2 days after surgery. Self-reported health status was measured on postoperative day 2 using a vertical visual analogue scale (VAS) marked 0-100 where 0 was the worst and 100 was the best health state that they could imagine (adopted from EuroQol group, www.euroqol.org). Time to readiness for discharge (TRD), defined as the time when the patient tolerates oral intake, has adequate pain control with oral analgesia, is able to mobilise, and has an acceptable clinical examination and laboratory test values, was recorded by an assessor blinded to group assignment (177). Postoperative complications and infections to 30-days were defined as per NSQIP (140, 141) and graded according to the Clavien-Dindo classification (178).

Statistical methods:

Sample size calculation- The study was designed to detect differences in intraoperative insulin resistance by assessing the amount of increase in the glucose infusion rate during HEC.

Based on a previous study on insulin resistance in colorectal surgery patients (61), a 20% decrease in insulin resistance (mean increase in postoperative glucose infusion rates during HEC of at least 0.42 mg/kg/min ± 0.35) would yield 80% power and 0.05% significance. The resultant sample size was calculated to be 12 patients per group for the study. To adjust for any surgery cancellations or drop-outs, we aimed to recruit 30 patients (15 per group). The 20% difference was chosen based on the original study from Nygren et al reporting a benefit for complex CHO drinks, in which the M value declined by 37% after fasting compared to a decline of 17% after the complex drink. In this study of 16 patients, the 17% decline was not considered clinically significant, nor was it statistically significant (179).

Statistical analysis- Between-group comparisons were performed using Chi square test (categorical data), independent t-test (continuous data, normally distributed) or Mann-Whitney U test (continuous data, not normally distributed). Significance was set at $P < 0.05$. Statistical analysis was conducted using STATA 12 (StataCorp, College Station, TX, USA). Data expressed as mean (SD) unless otherwise specified.

Results:

Baseline characteristics and risk factors:

A total of 149 consecutive patients were assessed for eligibility according to the exclusion/inclusion criteria with 30 recruited patients randomized to the study groups (15 to the simple CHO group and 15 to the complex CHO group)**.** One patient in the complex CHO group was excluded after randomization by the anesthesiologist who did not want HEC performed due to concerns about the patient's pulmonary issues (Figure 1). No harms or unintended effects were observed in the participants after receiving CHO drinks or undergoing study procedures.

Baseline characteristics and operating room variables are summarised in Table 1. The two groups were well balanced in terms of gender, BMI, ASA and comorbidities such as hypertension, malignancy and smoking. However, patients randomised to the simple CHO group were older (70 (10) vs 58(13) years, p=0.001).

Intraoperatively, the patients in both the simple and complex CHO groups had low residual gastric volumes (17(11) vs 19 (9.5) ml, p= 0.63). There were no differences in the types of procedures performed, OR time (median (IQR) 205(167-273) vs 166(145-235) minutes, p=0.84) or blood loss (median (IQR) 100(50-200) vs 100(75-250) ml, p=0.52).

Insulin sensitivity and glycemia:

Both groups reached euglycemia within approximately 90 minutes from the start of HEC procedure (95(37) vs 89(28) mins, p=0.63); there was no significant difference in the mean plasma glucose levels during HEC at each time point (Figure 2). There was no difference in the level of intraoperative whole body insulin sensitivity as assessed by HEC following ingestion of a simple or a complex CHO drink (M values 8.3(3.3) vs 8.8 (3.8) mg/kg/min, p=0.7; M values normalized to lean fat free body mass 0.15(0.07) vs 0.16(0.07), p=0.62). There was no difference in the proportion of patients with preserved intraoperative insulin sensitivity as defined by M values more than 5.5 mg/kg/min intra operatively (74% vs 79%, p= 1).

There were no differences in the HOMA2 indices (HOMA2-IR, HOMA2-%S, HOMA2-%B) between the two groups at baseline or on days 1 to 3 postoperatively (Table 2). The proportion of patients with insulin resistance defined by HOMA-IR cut-off values for men and women (2.06 in men and 1.95 in women) (175, 176) were comparable at all time points

following ingestion of a simple or a complex CHO drink (baseline- 0 vs 7%, p=0.48; POD1- 20% vs 14%, p=1; POD2- 20% vs 7%, p=0.5; POD3- 9% vs 0, p=0.4).

There were no differences in FBG levels at baseline (5.24(0.6) vs 5.23(0.34) mmol/L, p=0.9) or during the 3 days after surgery (Figure 2). Hyperglycemia, defined by FBG≥7 mmol/L, was only seen on POD1 and the proportion of patients with elevated FBG was similar in the simple and complex CHO groups (6(40%) vs 2(21%), p=0.4).

Other outcomes:

There were no differences in the CRP levels between the two groups at baseline or during the 3 days following surgery (Figure 2).

There were no differences between the simple and complex CHO groups in overall complications (5 (33%) vs 3 (21%), p= 0.7), severe complications (Clavien III-V) (3 (20%) vs 0, p= 0.2) or infection rates (2 (13%) vs 1 (7%), p= 1). There was also no difference between groups in time to readiness for discharge (median 2 (IQR 2-3) vs 2 (2-3) days, p=0.6) and length of hospital stay (median 3.5 (IQR 3-7) vs 2.5 (2-4) days, p= 0.1) (Table 3).

The percentage of reduction in the grip strength of the dominant hand on POD 2 was comparable between the simple and complex CHO groups (-8.3 (2.7) % vs -7.2 (3.4) %, p= 0.35). There was no difference in the health state VAS reported by the participants on POD2 (median (IQR) 70 (67.5-85) vs 80 (70-87.5), p=0.3).

Discussion:

Guidelines (180) encourage provision of CHO drink prior to colon resection based on moderate quality evidence available from recent systematic reviews and meta-analyses (72, 73).

However, these recommendations are based on evidence derived mostly from studies on preoperative provision of a drink containing complex CHO. In contrast, several high-volume centres recommend drinks containing simple CHO due to their higher availability and lower cost (21-22). In this randomised clinical trial, we compared perioperative insulin resistance after ingestion of a simple CHO drink and a complex CHO drink in nondiabetic patients undergoing elective laparoscopic colon resection in an established ERP. Insulin sensitivity was preserved in the intraoperative and postoperative periods in both groups. There was no difference between the groups who received simple versus complex CHO drink in whole body insulin sensitivity (measured by HEC) during the operation or the hepatic insulin resistance (measured by HOMA2-IR) in the first 3 days postoperatively.

The complex CHO drink in our study was prepared to closely reflect the content of the commercial CHO drink used in previous studies (PreOp®; 40 gr maltodextrin, 260 mOsm/kg, PH 4.9) (24, 61-63), which was not available in Canada at the time of study design. The simple CHO drink (Minute Maid® Without Pulp) had a much higher osmolality (648 mOsm/kg) and a lower PH of 3.7, which may potentially result in slower gastric emptying (181). However, in the current study, the gastric residual volume remained very low and comparable between complex and simple CHO drinks.

The peak insulin response within the first 60 minutes after ingestion of a simple CHO drink is only about half that of a complex CHO drink (181). However, simple CHO maintained the intraoperative insulin sensitivity at the same level as complex CHO drink despite inducing a lower insulin response peak. This might be due to the fact that reduced insulin sensitivity intra/postoperative is mostly the result of reduced glucose uptake by the peripheral tissue independent of the accumulated insulin response (22, 62). CHO drinks help maintain glucose

uptake by activating GLUT4 glucose transporters in muscles through the modulation of the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB) signalling pathway (15, 22, 65).

Reduced insulin sensitivity is the main element of disrupted glucose/protein metabolic hemostasis after surgery and is linked to postoperative hyperglycemia, increased complications, infections and length of stay (8). In the current study we employed HEC, the gold standard procedure to assess the intra-operative insulin sensitivity. In open elective major abdominal surgery, insulin sensitivity measured by HEC is reduced by up to 40% compared to baseline, regardless of preoperative carbohydrate loading (182). We were not able to compare preoperative insulin sensitivity to the intra-operative insulin sensitivity as we did not perform HEC preoperatively. However, intraoperative insulin sensitivity remained normal in both groups regardless of the type of CHO drink. The maintained insulin sensitivity may have been the result of the lower magnitude of surgical stress associated with laparoscopic versus open surgery (17). In addition, the patients were treated in an established ERP with high adherence to other perioperative interventions designed to reduce the surgical stress response and maintain insulin sensitivity (139).

Insulin sensitivity measured by HEC was preserved intraoperatively in both groups in the current study. This finding suggests that there were no additional benefits to provision of complex CHO preoperative versus simple CHO for enhancing intra operative insulin sensitivity. These results are consistent with evidence from a recent network meta-analysis which reported no significant difference in insulin sensitivity measured by HEC after provision of a complex CHO drink compared to placebo/water (73). The three randomised trials included in this meta-analysis studied patients undergoing hip replacement. Two of the studies found that insulin sensitivity was better preserved in patients who received complex CHO vs placebo (62, 63)

while the third study reported no difference (183). There is only one previous randomized study in open colorectal surgery using HEC to assess insulin sensitivity in patients receiving a preoperative complex CHO drink compared to fasting patients. This RCT, which was not included in the meta-analysis, reported significantly reduced insulin sensitivity on POD 1 compared to baseline in both patient groups; however, insulin sensitivity was less reduced in patients given CHO compared to an overnight fast (61).

While HEC is considered the most reliable technique reflecting whole-body sensitivity to insulin (172, 184), it is a complex and invasive test and was not performed at baseline in order to reduce the burden for patients. Instead, we used the HOMA2 model, a widely accepted non-invasive method (172, 185) to measure levels of resistance to insulin in clinical studies. HOMA2 is an updated computerized model which estimates insulin resistance (IR), beta-cell function (%B) and insulin sensitivity (%S) from fasting glucose and insulin levels (174, 186). Furthermore, insulin resistance following the first 24 hours after surgery is thought to be mostly due to hepatic insulin resistance (62). There was no difference in any of these indices of insulin resistance after ingestion of a simple or complex CHO drink on POD 1-3. This provides reassurance that the decision to measure only intraoperative insulin sensitivity using the gold standard HEC did not miss a relevant postoperative difference. Meta-analysis of previous studies employing HOMA to measure insulin resistance after a variety of types of procedures demonstrates a very slight but statistically significant decrease in insulin resistance after CHO loading compared to fasting or placebo (72, 73, 169). In previous studies however, there were wide confidence intervals and high inconsistency related to the wide variety of surgical procedures included, magnitude of surgical stress, and timing of measurement of insulin resistance.

There were no differences in postoperative fasting blood glucose between the two CHO drink groups. While a higher proportion of patients in the simples CHO group had FBG>7 on POD1 (40% vs 21%) this was not statistically significant. Furthermore, no patient in either group had a FBG>10, the level which has been shown to be associated with worse outcomes in nondiabetic patients (13). There was also no difference in clinical outcomes between the two CHO drink groups. While this study would not have been sufficiently powered to detect differences, this finding is consistent with previous work. A Cochrane review synthesizing the results of 27 trials of mostly complex CHO drinks compared to fasting on clinical outcomes showed a very slight benefit on reducing length of hospital stay with no impact on other postoperative outcomes, such as overall complications or infections. No benefit was observed when CHO drinks were compared to water or placebo (72). The more recent network meta-analysis also reported that CHO loading prior to surgery did not influence postoperative outcomes regardless of dose (73). A recent multicenter phase III clinical trial (PROCY trial) (66) reported that patients receiving preoperative complex CHO drinks had fewer occurrences of hyperglycemia postoperatively compared to placebo, but with no impact on infection rates after surgery. Despite this limited evidence, the latest recommendation from the ERAS Society (2019) strongly recommends preoperative carbohydrate drinks and upgraded the quality of evidence to low from very low (58).

The current double-blinded randomized clinical trial has several strengths. It is the first randomized comparison of complex or simple CHO in patients undergoing laparoscopic colectomy within an ERP setting. Participants were screened by their HbA1c level to eliminate the possible confounding impact of baseline insulin resistance on the perioperative metabolic state. In addition, by excluding the cases with new stoma formation or rectal surgeries, the

surgical population in the current RCT had a more or less consistent level of surgical stress at least according to their type of operation. The outcomes assessors, patients, surgeons and anesthesiologists were blinded to treatment allocation. Also, importantly, intra-operative insulin sensitivity was measured using the gold standard technique of HEC.

The current study also has some limitations. The study sample size is relatively small, but was appropriately powered to find a 20% difference in M value between the groups, based on the seminal work from Ljungqvist et al, where a 17% decrease in M value after complex CHO was not statistically or clinically significant (179). Furthermore, the M value for both groups was well above 5.5mg/kg/min indicating no insulin resistance; consequently, any undetected (Type II error) percentage difference between the groups (if any) would not be clinically relevant. The relatively high degree of diabetes/pre-diabetes resulted in the exclusion of almost one-third of the screened patients. This might reduce the applicability of the results to a more heterogeneous population. While there is no additional benefit for complex CHO versus simple CHO for enhancing intra/postoperative insulin sensitivity in nondiabetic patients, the effects of such drinks in pre/diabetes needs to be further studied. Patients receiving the simple CHO drink group were older and we cannot completely rule out any age-related degree of basal insulin resistance, however there were no differences in HBA1c levels or HOMA2-IR at baseline. Assessment of HEC was only performed intra-operatively; hence, we were not able to assess and compare the whole-body insulin sensitivity (peripheral tissue glucose uptake) at baseline or postoperatively. Our postoperative assessment was limited to changes in hepatic insulin resistance. The reduction in insulin sensitivity is believed to peak on POD 1 as a result of reduced glucose disposal at the peripheral tissue level; this reduction may have been underestimated intraoperatively and by the postoperative assessment of HOMA2-IR, an estimate of hepatic insulin resistance. In addition,

maintaining normoglycemia intraoperatively by HEC can itself reduce insulin resistance and complications after some types of surgery (148). Finally, the subjects underwent laparoscopic colectomy in a well-established ERP, with high adherence to other perioperative interventions (139) that may have also helped maintain insulin sensitivity.

Conclusion:

In nondiabetic patients undergoing elective laparoscopic colon resection, intra and postoperative insulin sensitivity was preserved and there was no additional benefit of ingesting a preoperative drink containing complex CHO compared to a simple CHO. In this patient population, either drink may be used. Whether these results are applicable to other patient populations requires further study.

Figure 1 – Consort diagram

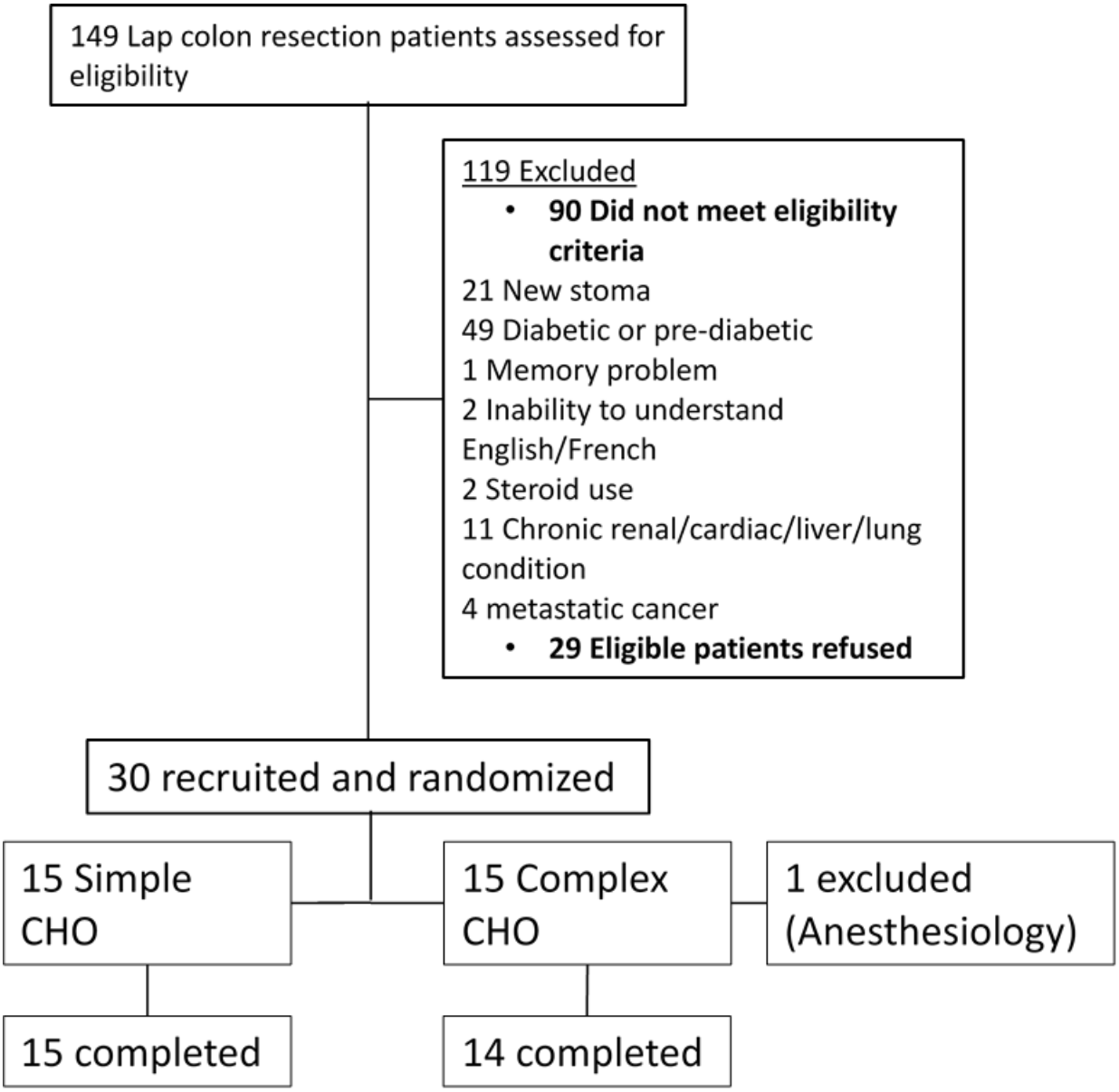


Figure 2 – Plasma glucose levels during hyperinsulinemic euglycemic clamp

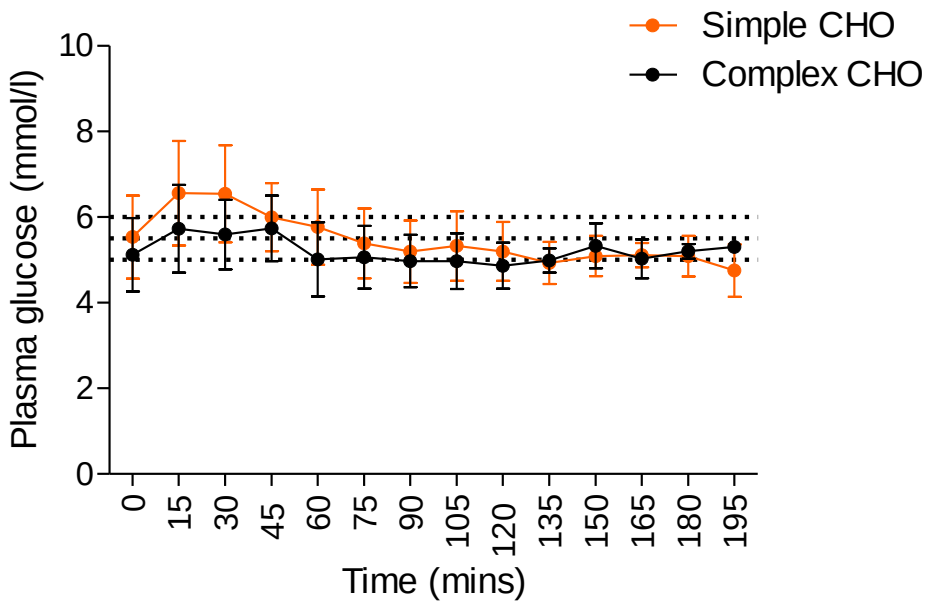
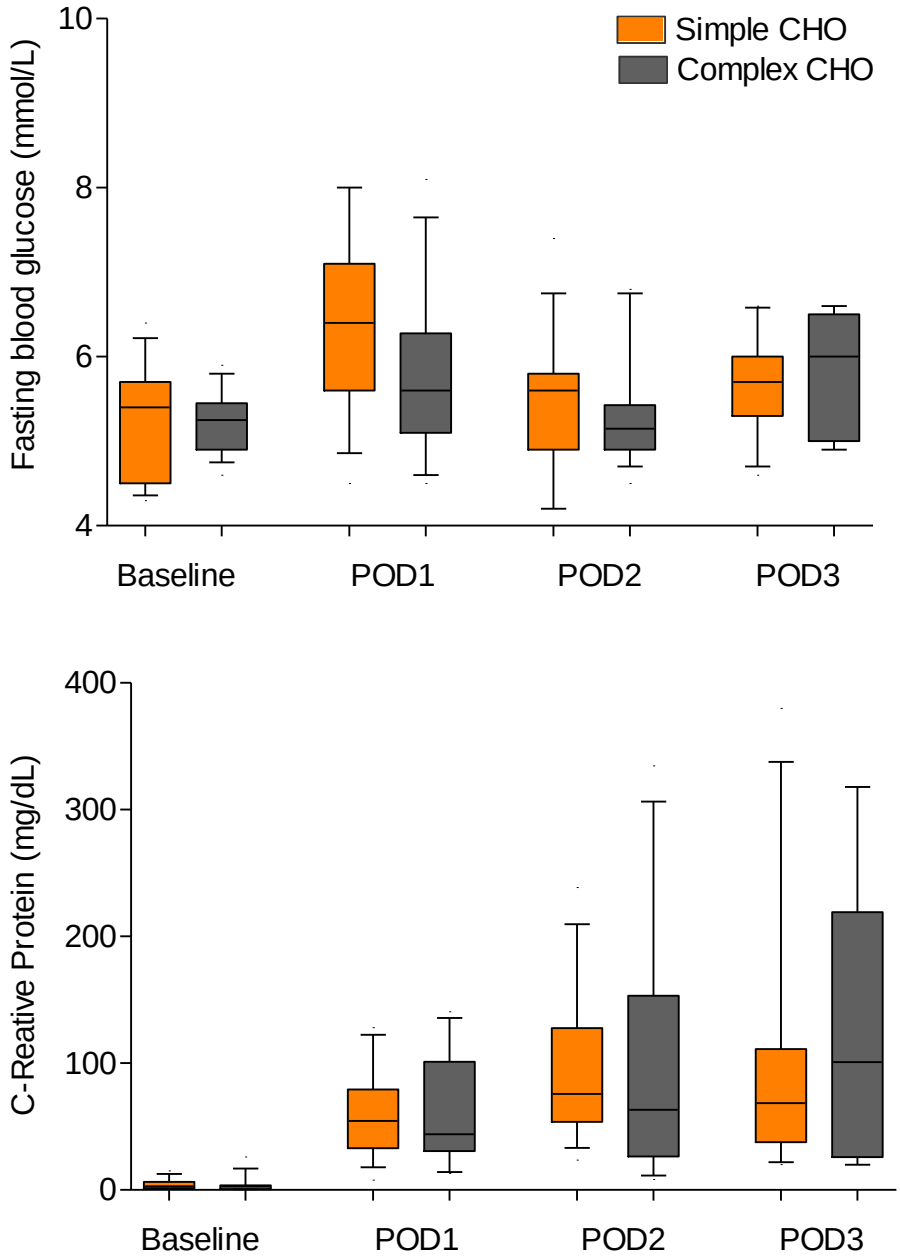


Figure 3 – Perioperative fasting blood glucose and C-reactive protein



Perioperative fasting blood glucose (FBG) and C-reactive protein (CRP) levels compared between nondiabetic patients who received simple CHO (fructose) versus complex CHO (maltodextrin); p value <0.05 was considered significant.

Table 1- Baseline characteristics and clinical risk factors

Variables	Simple CHO (n=15)	Complex CHO (n=14)	P value
Age, mean (SD)	70(10)	58(13)	0.001
Female	5(33)	7(50)	0.45
BMI (Kg/m2), mean (SD)	27.2(5.5)	25.5 (5.3)	0.41
HbA1c	5.4(0.3)	5.2(0.3)	0.23
ASA			1
I-II	14(93)	14(100)	
III or IV	1(7)	-	
Charlson index, mean (SD)	1.73(0.7)	1.14(1.03)	0.08
Hypertension	9(60)	6(43)	0.46
Current smoker	5(33)	6(43)	1
Malignancy	13(90)	9 (64)	0.21
Type of procedure			
Right hemicolectomy	5(33)	4(29)	1
Left hemicolectomy	2(13)	-	0.48
Sigmoid resection	8(53)	6(43)	0.71
Ileocecal resection	-	3(21)	0.09
Transverse colectomy	-	1(7)	0.48
OR time (minutes), median (IQR)	205(167-273)	166(145-235)	0.84
Blood loss (ml), median (IQR)	100(50-200)	100(75-250)	0.52
Intra-operative blood transfusion	0	0	-
Gastric fluid residue (ml), mean(SD)	17.1(10.6)	18.9 (9.5)	0.63

Data expressed as number of patients (%) unless specified.

Table 2- Postoperative insulin resistance (HOMA2-IR), insulin sensitivity (%S) and B-cell function (%B)

Variables	Simple CHO (n=15)	Complex CHO (n=14)	P value
HOMA2-IR			
Baseline	0.84(0.41)	0.98(0.61)	0.49
POD1	1.59(1.11)	1.2(0.99)	0.33
POD2	1.37(1.13)	1.15(0.48)	0.51
POD3	1.07 (0.56)	1.17(0.55)	0.72
HOMA2-%S			
Baseline	130.2(101-167)	123.3(83-182)	0.80
POD1	84(56.5-125)	107.4(70.5-163.5)	0.37
POD2	101.5(64-160)	94(73-120.5)	0.75
POD3	103.6(76-141)	96(58-158)	0.76
HOMA2-%B			
Baseline	73.2(64.5-83)	75(56-100)	0.87
POD1	66.5(51.5-86)	69(51-92)	0.85
POD2	80.7(65-100)	87.3-74-103)	0.53
POD3	71.7(60.5-85)	73.8(63.5-86)	0.77

HOMA2-B% and HOMA2-%S sensitivity are reported as geometric mean ± 95% CI; p value <0.05 was considered significant.

Table 3- Postoperative outcomes

Variables	Simple CHO (n=15)	Complex CHO (n=14)	P value
Any complication	5(33)	3(21)	0.68
Infectious complications	2(13)	1(7)	1
Any SSI	2(13)	1(7)	1
Incisional	0	1(7)	0.48
Organ space	2(13)	0	0.48
Urinary tract infection	0	0	-
Sepsis	1(6)	0	1
Pneumonia	1(6)	0	1
Other infections	1(6)	0	1
Surgical complications	2(13)	1(7)	1
Anastomotic leak	2(13)	0	0.48
Ileus	0	1(7)	0.48
Other surgical complications	0	0	-
Respiratory complications	2(13)	0	0.48
Cardiac complications	0	0	-
Deep vein thrombosis	0	0	-
Acute renal insufficiency	0	0	-
Complication severity (highest grade)			
Clavien I-II	2(13)	3(21)	0.65
Clavien III-IV	3(20)	0	0.22
Death	0	0	-
Time to readiness for discharge (days), median(IQR)	2(2-3)	2(2-3)	0.62
Primary length of stay (days), median(IQR)	2(2-3)	2.5(2-4)	0.61
Readmissions	2(13)	0	0.48
Total length of stay (days), median(IQR)	3.5(3-7)	2.5(2-4)	0.1

Data expressed as number of patients (%) unless specified. SSI= surgical site infection

Appendix 1:

Inclusion Criteria:

1- At least 18 years of age

2- Planned laparoscopic partial colon resection for non-metastatic neoplastic or benign disease (including right, transverse, left or sigmoid))

3- HbA1c less than or equal to 5.7%

4- Not receiving any kind of glucose lowering medication.

Exclusion Criteria:

1-Are already diagnosed with diabetes or pre diabetes (HbA1c > 5.7%)

2-Are pre-diabetic receiving glucose lowering intervention

3-Have renal or liver dysfunction

4-Will undergo extended resection of adjacent organs

5-Non-elective operations

6-New stoma created

7-Have conditions precluding participation in the ERAS

8- Have conditions requiring preoperative fasting

9- Have cardiac abnormalities, severe end-organ disease

10- Have received steroids for longer than 30 days

11- Have poor English or French comprehension.

CHAPTER 4: SUMMARY AND CONCLUSIONS

4.1 General findings:

Surgical trauma triggers a cascade of events that results in insulin resistance and hyperglycemia (18, 166). Insulin resistance and hyperglycemia are both linked to increased postoperative infections and morbidity. Thus, risk stratification to identify patients at risk for perioperative insulin resistance, and providing evidence-based interventions to maintain insulin sensitivity, are both key strategies to improve safety and quality in surgery.

The aim of this dissertation was first to better understand the role of preoperative HbA1c screening, an indicator of baseline insulin resistance, as a preoperative risk stratifying strategy for identifying nondiabetic patients at increased risk of developing postoperative complications. A systematic review of the literature investigating the relationship between preoperative HbA1c and outcomes in nondiabetic patients undergoing various types of surgical procedures was performed (135). In this synthesis of 6 previous studies including 14,363 patients (chapter 2.2), elevated HbA1c (generally defined as >6%) was associated with an increased risk of postoperative complications after colorectal, bariatric, vascular and cardiac surgery. However, we identified only one previous study in colorectal surgery patients, which was limited by not having an upper cutoff for HbA1c (i.e. not excluding patients with undiagnosed diabetes). In addition, this study was in the context of major open colorectal surgery.

To address the limited evidence for use of HbA1c as a screening tool in nondiabetic patients undergoing laparoscopic colorectal surgery, we studied a novel cohort of patients (chapter 2.4). The prevalence of prediabetes was 34%, consistent with the previously reported range of 11% to 32% in noncardiac surgery populations (40, 99, 147). In contrast to the previous study, we did not find any association between elevated preoperative HbA1c level and perioperative hyperglycemia, postoperative complications, infections or length of hospital stay in

these patients. We questioned whether the lack of an association between preoperative insulin resistance and postoperative outcomes suggested that insulin sensitivity was being maintained perioperatively when laparoscopic surgery and an Enhanced Recovery Program were being used.

This led us to investigate whether the use of preoperative oral complex CHO loading, a strategy designed to modulate perioperative insulin resistance, remained beneficial in the era of laparoscopic surgery. Simple CHO drinks are used by several leading North American centres. However, because of differences in their glycemic indexes the insulin response after simple CHO is known to be less than complex CHO (69, 71). Whey protein, as an abundant source of essential branched-chain amino acids (BCAAs) with insulinotropic properties, may be able to boost the insulin response after simple CHO drinks (76, 77). We first investigated the insulin response after simple CHO with the addition of whey protein and found that whey protein cannot increase the level of triggered insulin response triggered by simple CHO drinks.

The peak insulin response to simple CHO was approximately half of the previously reported peak insulin after ingestion of complex CHO ((215-264 pmol/l vs 451 pmol/l) (67) and the addition of whey protein did not have an impact. However, whether this lower insulin response would impact perioperative insulin sensitivity was not known.

Therefore, we performed a randomized controlled trial (chapter 3.4) to compare the effects of simple versus complex CHO drinks on intra and postoperative insulin sensitivity in patients undergoing laparoscopic colorectal surgery. Employing the gold standard technique hyperinsulinemic euglycemic clamp and HOMA index to measure insulin sensitivity we demonstrated, in contrast to previous studies, preservation of intra and postoperative insulin sensitivity in this population; in fact, intraoperative M values for both the simple and complex CHO drink groups stayed well above 5.5 mg/kg/min, the cutoff for insulin resistance. Similarly,

the proportion of patients with postoperative HOMA-IR values above the cut-offs defining insulin resistance were comparable following ingestion of a simple or a complex CHO drink

There was no difference between the two groups in any other postoperative outcomes such as postoperative complications, infections or length of hospital stay. We did not find any additional benefit to provision of complex CHO drink compared to simple CHO drink in enhancing the intra and postoperative insulin sensitivity in patients undergoing elective laparoscopic colon resection.

4.2 Limitations:

This dissertation had several limitations which should be considered in interpretation of results and conclusions.

Very few studies were found eligible for inclusion in the systematic review in chapter 2.2.; this limited the strength of the overall conclusion and applicability of the results specifically to other patient populations. Furthermore, inclusion of emergency cases and patients with HbA1c levels above 6.5 %, the cut off for diagnosis of diabetes in some studies, made it even harder to draw strong conclusive evidence from the systematic review.

The patients in the prospective cohort study in chapter 2.4 were being screened for a randomized controlled trail (chapter 3.4) in which only patients scheduled to undergo elective laparoscopic surgery within an ERP were included. Therefore, the results of the current study may not be applicable to open colorectal surgery or emergency cases, or institutions using traditional perioperative care rather than an ERP. The proportion of patients with complications especially infectious complications was unexpectedly low in this study compared to previous reports of 20% in the colorectal patients in our center (35) and the study was therefore

underpowered which might have limited its ability to detect differences with this very low rate of postoperative infections between patients with normal and elevated HbA1c levels. A considerable number of patients did not have perioperative random blood glucose values recorded, therefore the sample size to assess the association of preoperative HbA1c levels with postoperative elevated RBG levels was even smaller. Also, random blood glucose is of limited value in reflecting the true metabolic status of patients compared to fasting blood glucose (40).

The study in chapter 3.2 was limited by enrolling healthy volunteers instead of surgical patients. The cross over design of this study reduced the sample size requirements by decreasing between-individual variability, however, due to presence of outliers at different time points we cannot rule out the possibility of type II error in the findings. Also another arm in the study to receive complex CHO drink would have been very informative and beneficial in better understanding the differences in the triggered insulin responses after simple versus complex CHO drinks.

The high prevalence of prediabetes in the patient population screened for the control randomized trial in chapter 3.4 resulted in a high exclusion rate for the RCT and this limits the generalizability to a more heterogeneous surgical population. It should therefore be considered an efficacy trial rather than an effectiveness trial (187). In addition the participants underwent the surgical procedures in a well-established Enhanced Recovery Pathway with a high level of adherence (139) which can modify insulin sensitivity. The other limitation of this RCT was that we only performed hyperinsulinemic euglycemic clamp to measure insulin sensitivity intraoperatively which precluded our ability to compare the pre and postoperative metabolic condition of patients. We addressed this limitation by employing HOMA2-IR pre and postoperative, however, HOMA2-IR is an estimate of hepatic insulin resistance and might have

underestimated the postoperative insulin resistance in the peripheral tissue which usually peaks around postoperative day1. Finally while we cannot rule out the confounding effect of age differences between the two groups on baseline insulin resistance, we tried to minimize the impact of baseline differences by screening patients according to their preoperative HbA1c levels to exclude patients with prediabetes.

4.3 Future directions:

While according to our results screening for HbA1c level preoperatively is not recommended prior to elective laparoscopic colon resection patients, there is limited evidence investigating the value of HbA1c (93) in diagnosing and predicting insulin resistance in other surgical population.

In the randomized trial, we focused on patients without diabetes. While there is evidence supporting the safety of complex CHO drinks in diabetic patients without risk of hyperglycemia (163, 188), the evidence for the benefits of either complex or simple CHO drinks in either diabetes or prediabetes is very limited (189). Therefore, the effects of such drinks in pre/diabetes needs to be further studied. The randomized controlled trial in chapter 3.3 was an efficacy study in the specific population of nondiabetic elective laparoscopic colon resection patients which may not be applicable to other populations, warranting further studies in other open and laparoscopic surgical populations. In addition, the fact that insulin sensitivity was preserved in both groups leads to the question of whether any CHO drink is required.

Our results showed the limited ability of additional whey protein in enhancing the insulin response triggered by simple CHO drinks. However, different combinations of preoperative drinks containing simple/ complex CHO plus other protein based supplements might produce

various effects on intra and postoperative insulin sensitivity in different surgical procedures which should be further explored.

4.4 Conclusions:

While there might be an association of preoperative HbA1c level with postoperative outcomes, in the laparoscopic colon resection patients there is no association between elevated preoperative HbA1c level and postoperative infections and preoperative screening for HbA1c level is not recommended in this population.

The peak insulin response to simple CHO is lower than complex CHO drink and the addition of whey protein did not enhance it in the healthy individuals. There is no additional benefit for preoperative provision of a drink containing complex CHO compared to simple CHO in nondiabetic patients undergoing laparoscopic colon resection due to preserved intra and postoperative insulin sensitivity; therefor either drink could be used in this setting.

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