Perioperative Glycemic Control in Vascular Surgery

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Table of Contents

List of Figures and Tables*

**Does not include Tables and Figures contained within Manuscripts*

List of Abbreviations

MUHC (McGill University Health Centre)
LDL (Low-density Lipoprotein)
Apo-B (Apolipoprotein B)
PAD (Peripheral Arterial Disease)
CLTI (Chronic Limb-threatening Ischemia)
SSI (Surgical Site Infection)
HbA1c (Hemoglobin A1c)
IL-1ß (Interleukin 1 beta)
IL-8 (Interleukin 8)
EMR (Electronic Medical Record)
MACE (Major Adverse Cardiac Events)
MALE (Major Adverse Limb Events)
ABI (Ankle-Brachial Index)
TP (Toe Pressure)
ESRD (End Stage Renal Disease)
CAD (Coronary Artery Disease)
CKD (Chronic Kidney Disease)
BMI (Body Mass Index)
COPD (Chronic Obstructive Pulmonary Disease)
CHF (Congestive Heart Failure)
ER (Emergency Room)
ICU (Intensive Care Unit)
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses)
ROBINS-I (Risk of Bias in Non-Randomized Studies of Interventions)

1 Abstract - English

Introduction: Perioperative hyperglycemia occurs frequently and is associated with perioperative morbidity and mortality following vascular surgery. We sought to examine current glycemic surveillance and control patterns at the McGill University Health Centre (MUHC) and the impact of perioperative hyperglycemia on outcomes following vascular surgery. We also examined the literature on the use of one glycemic control intervention, intensive insulin therapy, for pre-existing studies performing this intervention on patients undergoing lower extremity vascular surgery.

Methods: Current glycemic control patterns at the MUHC were evaluated by retrospective data collection on patients who underwent open infrainguinal vascular surgery. Patient baseline characteristics, intra-operative factors, efficacy of glycemic control, and post-operative outcomes were assessed using univariate and multivariate analysis.

A systematic review was then performed to determine the evidence for the use of intensive insulin therapy to reduce the risk of complications following open lower extremity vascular surgery.

Results: 38.9% of patients experienced perioperative hyperglycemia defined as glucose ≥ 10 mmol/L during their hospital admission. Only 3.9% of patients within the cohort underwent any intraoperative glycemic surveillance, despite the fact that 43.9% of patients were diabetic. 16.8% patients remained hyperglycemic for at least 40% of their measurements during their hospitalization. Multivariable logistic regression including the covariates of age, sex, hypertension, smoking status, diabetic status, presence of chronic kidney disease, dialysis, Rutherford stage, coronary artery disease and perioperative hyperglycemia demonstrated a significant relationship between perioperative hyperglycemia and 30-day mortality (OR 25.00,

95% CI 2.469 – 250.00, p = 0.006), major adverse cardiac events (OR 2.08, 95% CI 1.008 - 4.292, p = 0.048), major adverse limb events (OR 2.24, 95% CI 1.020 – 4.950, p = 0.045), acute kidney injury (OR 7.58, 95% CI 3.021 – 19.231, p <0.001), reintervention (OR 2.06, 95% CI 1.117 - 3.802, p = 0.021) and intensive care unit admission (OR 3.38, 95% CI 1.225 – 9.345, p = 0.019).

A systematic literature review identified two studies using intensive insulin therapy during and immediately following vascular surgery. Protocols for insulin infusion varied significantly and many patients did not achieve normoglycemia. Studies were also underpowered.

Conclusion: Perioperative glycemic monitoring and control is sub-optimal following lower extremity revascularization and is associated with significant morbidity and mortality in our cohort. Pre-existing literature on the use of intensive insulin therapy in the perioperative period in patients undergoing vascular surgery are underpowered and too variable to allow conclusions on the safety and efficacy of intensive insulin therapy to be drawn.

More consistent monitoring and the use of more effective glycemic control protocols at the McGill University Health Centre, such as the use of an intensive insulin protocol, might provide a yet unexplored avenue for reducing patient morbidity and mortality following lower extremity open vascular surgery. Further studies on the use of intensive insulin therapy in patients undergoing lower extremity revascularization or major amputation are needed to properly assess this intervention.

2 Abstract - French

Introduction : L'hyperglycémie périopératoire est fréquente et est associée à la morbidité périopératoire, notamment à l'infection du site chirurgical après une chirurgie vasculaire. On a constaté que l'insulinothérapie intensive diminue le risque de complications dans d'autres spécialités chirurgicales, comme la chirurgie cardiaque. Nous avons cherché à examiner les modèles actuels de surveillance et de contrôle de la glycémie au Centre universitaire de santé McGill et l'impact de l'hyperglycémie périopératoire sur les risques de complications après une chirurgie vasculaire. Enfin, nous avons examiné la littérature sur l'utilisation d'une intervention de contrôle de la glycémie, l'insulinothérapie intensive, pour les études préexistantes qui ont réalisé cette intervention sur des patients subissant une chirurgie vasculaire.

Méthodes: Les modèles actuels de contrôle de la glycémie à utilisés au Centre universitaire de santé McGill ont été évalués rétrospectivement sur des patients qui ont subi une chirurgie vasculaire infra-inguinale ouverte. Les caractéristiques de base des patients, les facteurs peropératoires, l'efficacité du contrôle de la glycémie et les résultats postopératoires ont été évalués à l'aide d'une analyse univariée et multivariée. Une revue systématique a été effectuée pour déterminer les preuves de l'utilisation d'une insulinothérapie intensive pour réduire le risque de complications après une chirurgie vasculaire ouverte des extrémités inférieures.

Résultats : 38,9 % des patients ont présenté une hyperglycémie péri-opératoire définie par un taux de glucose de ≥ 10 mmol/L pendant leur hospitalisation. Seuls 3,9 % des patients de la cohorte ont fait l'objet d'une surveillance glycémique peropératoire. 16,8 % des patients sont restés hyperglycémiques pendant au moins 40 % de leurs mesures au cours de leur hospitalisation. Une

régression logistique multivariable incluant les covariables de l'âge, du sexe, de l'hypertension, du tabagisme, du diabète, de la présence d'une maladie rénale chronique, de la dialyse, du stade de Rutherford, de la coronaropathie et de l'hyperglycémie périopératoire a démontré une relation significative entre l'hyperglycémie périopératoire et la mortalité à 30 jours (OR 25.00, 95% CI 2.469 - 250. 00, p = 0,006), les événements cardiaques indésirables majeurs (OR 2,08, IC 95 % 1,008 - 4,292, p = 0,048), les événements majeurs affectants les membres inférieures (OR 2,24, IC 95 % 1,020 - 4,950, p = 0,045), les lésions rénales aiguës (OR 7.58, 95% CI 3.021 – 19.231, p <0.001). Une revue systématique de deux études ayant rencontré l'utilisation d'une insulinothérapie intensive pendant et immédiatement après une chirurgie vasculaire a été identifiée. Les protocoles de perfusion d'insuline variaient considérablement et de nombreux patients n'ont pas atteint une normoglycémie. Les études étaient également sous-puissantes.

Conclusion : La surveillance et le contrôle de la glycémie périopératoire restent sous-optimaux après une revascularisation des membres inférieurs et sont associés à une morbidité et une mortalité significative. La littérature préexistante sur l'utilisation de l'insulinothérapie intensive en période péri-opératoire vasculaire n'est pas assez puissante et trop variable pour permettre de tirer des conclusions sur la sécurité et l'efficacité de l'insulinothérapie intensive. Une surveillance plus fréquente et l'utilisation de protocoles de contrôle glycémique plus efficaces, comme l'utilisation d'un protocole d'insuline intensive au Centre universitaire de santé McGill, pourraient constituer une voie encore inexplorée pour réduire la morbidité et la mortalité des patients après une chirurgie vasculaire ouverte des extrémités inférieures. D'autres études sur l'utilisation de l'insulinothérapie intensive chez les patients subissant une revascularisation des

extrémités inférieures ou une amputation majeure sont nécessaires pour évaluer correctement cette intervention.

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4 Contribution of Authors

All chapters in this thesis were authored by Dr. Anna Kinio and reviewed and edited by Dr. Heather Gill.

For the manuscript, *Perioperative Glycemic Surveillance and Control – Current Practices, Efficacy and Impact on Post-Operative Outcomes following Infra-inguinal Vascular Intervention,* Dr. Anna Kinio performed study design, data collection, analysis and manuscript preparation under the supervision of Dr. Heather Gill. Morgan Gold assisted with data collection and manuscript preparation. Dr. Robert James Doonan assisted with data analysis and manuscript preparation. Drs. Orent Steinmetz, Kent Mackenzie, Daniel Obrand, Elie Girsowicz and Jason Bayne assisted with manuscript preparation.

For the manuscript, *A systematic review on the impact of strict perioperative glycemic control on surgical site infections following lower extremity vascular surgery,* Dr. Anna Kinio performed the study design, was one of the independent reviewers and performed data collation, analysis and manuscript preparation under the supervision of Dr. Heather Gill. Joanne Abi-Jaoudé assisted with study design, wrote the search strategy, acted as a reviewer and assisted with manuscript preparation. Dr. Ahmed Naiem acted as an independent reviewer.

5 Introduction

5.1 Atherosclerosis

5.1.1 Pathogenesis of Atherosclerosis

Atherosclerosis refers to the chronic inflammatory process resulting in the build-up of subendothelial plaques in the arterial wall, often in areas with disturbed laminar flow, such as branch points or bifurcations.[1] The process is primarily driven by elevated levels of circulating cholesterol, also known as low-density lipoprotein (LDL) which are sequestrated by the transport protein apolipoprotein B (apo-B). Endothelial injury allows for the binding the apo-B-LDL complex to matrix proteoglycans in the arterial wall, leading to the accumulation of cholesterol between the endothelium of the arterial intima and the smooth muscle cells of the media.[1,2] These particles in turn become oxidized by reactive oxygen species, leading to the secretion of chemokines and adhesion molecules which lead to immune cell recruitment. The resulting mixture is comprised of a combination of cellular waste, apoptotic cells and lipids covered by a fibrous layer composed of collagen and smooth muscle cells.[2] Clinical symptoms result when the plaque causes luminal narrowing of the artery, leading to a significant stenosis and downstream tissue hypoxia, or due to acute plaque rupture causing thrombosis and vessel occlusion.[3]

5.1.2 Contributors to Atherosclerosis

Major determinants of atherosclerotic disease include non-modifiable and modifiable risk factors, all of which contribute in variations to the pathogenesis of the disease characterized by long latent periods, inflammation and accumulation of fatty deposits within the arterial lumen as well as sudden plaque rupture and thrombosis.

Increasing age, male sex and race have all been found to contribute to the development of atherosclerosis and have been linked to higher rates of cerebrovascular and myocardial infarctions.[5-7]

Modifiable risk factors determine risk of disease by modulating various aspects of the pathogenesis of atherosclerotic disease. Exposure to air pollution or cigarette smoking for example contribute to systemic inflammation, endothelial dysfunction and increased platelet activity.[8] Similarly, diet can increase risk by promoting high adiposity, the development of chronic atherosclerosis-promoting diseases such as diabetes mellitus or interestingly, by indirect pathways such as their influence on the microbiome.[9,10]

Diabetes mellitus is another risk factor which promotes multiple facets of atherosclerosis. Chronically raised blood glucose causes dyslipidemia, microvascular dysfunction, dysregulates the immune system to promote a state of chronic inflammation and encourages a pro-thrombotic state.[11] Similarly, chronic kidney disease contributes to hypertension, high cholesterol levels and dysregulation of calcium-phosphate metabolism, promoting calcification of atherosclerotic plaques.[12,13]

5.1.3 Clinical Manifestations of Atherosclerosis

Ultimately, atherosclerosis is a systemic disease, with clinical syndrome manifestation depending on the vascular territory involved. Presentation can be acute secondary to plaque rupture, or chronic due to progressive vessel narrowing.

This partially explains why patients with peripheral arterial disease have elevated cardiovascular and cerebrovascular mortality. Atherosclerotic disease in the lower extremity is only one manifestation of a systemic disease. Indeed even patients diagnosed without overt

cardiac disease have a 30% risk of myocardial infarction or stroke following a diagnosis of peripheral arterial disease.[14] This manifestation of symptoms or acknowledgement of disease in more than one vascular bed has recently been provided with the term "polyvascular disease" and acknowledges the elevated risk of co-existing vascular complications such as myocardial infarction or stroke, even in the absence of previous coronary or cerebrovascular disease diagnosis.[15]

5.2 Peripheral Arterial Disease

Peripheral arterial disease (PAD) is defined as atherosclerotic occlusive disease occurring in the upper or lower extremity arterial systems.[16] The build-up of arterial plaque occurs over decades but symptoms begin to manifest when the stenosis or occlusion of the arterial lumen causes tissue hypoxia by limiting blood flow to the extremity. This manifests as muscular pain initially only with exercise but can later progress to pain at rest or tissue loss.

Globally it is estimated that over 200 million individuals are diagnosed or affected by peripheral arterial disease, partially owing to an aging population as well as an increased prevalence of risk factors including smoking, hypertension, and diabetes.[17] PAD represents a major cause of disability in seniors due to a loss of independence caused by lower extremity pain or limb loss, and is associated with increased mortality due to a high risk of cardio and cerebrovascular events.[18]

5.2.1 Risk Factors for Peripheral Arterial Disease

PAD refers to atherosclerosis occurring in the arteries of the extremities. Most of the risk factors for the development of PAD therefore overlap with risk factors for other atherosclerotic disease processes. For instance, up to 68% of patients with arterial disease in one literature

review were found to have significant atherosclerotic disease in at least one other vascular bed.[19] As such, 5-year mortality for patients diagnosed with peripheral arterial disease is around 30%, primarily due to myocardial infarction or ischemic stroke.[20]

Demographic, or non-modifiable risk factors for PAD include age, race, low socioeconomic status and male sex. Of these, age plays the strongest role, with up to 30% of individuals in their eighth decade diagnosed with PAD in one observational study.[21]

Modifiable risk factors for PAD include cigarette smoking, hypertension, diabetes, hyperlipidemia and elevated serum homocysteine. Modification of these risk factors play an important role, not only for attenuating the progression of PAD but also for reducing the risk of atherosclerotic disease processes.

5.2.2 Clinical Presentation of Peripheral Arterial Disease

Peripheral arterial disease encompasses a spectrum of symptoms and clinical presentations ranging from asymptomatic to limb loss. One classification system seeking to prognosticate the risk of limb loss and aid in treatment decisions is the Rutherford classification (Table 1).[22] Using a combination of physiologic measurements and clinical presentation patients are organized into Grades 0 to 6.

Grade 0 patients fall into the category of patients that have asymptomatic peripheral arterial disease. Population-based studies have demonstrated that most patients with PAD fall into this category and are often only identified incidentally.[23] These individuals may lack symptoms due to a minimal burden of disease, or because of the anatomic location of atherosclerosis. Alternatively, a sedentary lifestyle may mask demand-ischemia in limbs. Finally, the development of collateral vessels allowing for continued downstream limb perfusion

despite the presence of stenosis or occlusion of an artery may also explain a lack of symptoms. While asymptomatic PAD continues to carry an elevated risk of cardiovascular events and mortality, risk of limb loss is relatively low.[24] Treatment in these patients therefore focuses on medical and lifestyle management of modifiable risk factors rather than surgical revascularization of the limb.

Grade	Category	Clinical Description	Objective Criteria
0	0	Asymptomatic	Normal treadmill or reactive hyperemia test
	1	Mild Claudication	Able to complete treadmill exercise; AP after exercise > 50 mmHg but at least 20 mmHg lower than at rest
I	2	Moderate Claudication	Between Rutherford 1 and 3 categories
	3	Severe Claudication	Cannot complete treadmill exercise and AP after exercise < 50 mmHg
II	4	Rest Pain	Resting AP < 40 mmHg and/or TP < 30 mmHg, PVR barely pulsatile or flat
III	5	Minor tissue loss (Non-healing ulcer, focal gangrene with diffuse pedal ischemia	Resting AP < 60 mmHg and/or TP < 40 mmHg, PVR barely pulsatile or flat
	6	Major tissue loss extending beyond the transmetatarsal level, functional foot no longer salvageable	Same as category 5

AP: Ankle Pressure; TP: Toe Pressure; PVR: Pulse Volume Recording

Table 1 Rutherford Clinical Categories of Chronic Limb Ischemia. Adapted from Rutherford et al., Journal of Vascular Surgery, 1997.

Intermittent claudication (Rutherford grades 1 to 3) refers to ischemic and reproducible buttock, hip, thigh or calf pain which occurs with activity and dissipates with rest.[24] This reflects demand ischemia of the muscle with exercise, where blood and oxygen delivery to exercising tissues with increased demands is impaired due to vessel stenoses and blockages. Risk of limb loss remains low (risk of major limb amputation of approximately 1% per year) in these

categories, and therefore medical and lifestyle modifications remain the mainstay of treatment.[25] Revascularization of the limb is considered only in select individuals with significantly impaired quality of life, anatomically favourable disease, and low surgical risk.

Rutherford grades 4 to 6 represent a significant increase in the risk of limb loss and are therefore encompassed by the term chronic limb-threatening ischemia (CLTI).[24] Patients with CLTI have severe disturbances in limb perfusion that fail to meet tissue oxygen requirements even when at rest. These patients present with ischemic pain at rest which may progress to tissue loss or non-healing wounds within the extremity. These patients are at higher risk of limb loss and are generally considered for prompt surgical revascularization.

5.2.3 Treatment of Peripheral Arterial Disease

PAD treatment is personalized to each patient and takes into account disease severity, patient fitness, and goals of care. Medication, lifestyle modifications, and surgical interventions are often combined with the goals of limb salvage, improved patient quality of life, and reducing the risk of cardio- and cerebrovascular morbidity and mortality.

Lifestyle changes such as smoking cessation, regular exercise, and a healthy diet should be promoted for all patients with PAD. In patients with intermittent claudication alone, regular walking has been shown to increase pain-free walking distance and decrease functional decline without the need for surgical revascularization.[26,27]

Blood pressure, blood glucose, and dyslipidemia should be controlled. Antiplatelet agents are also frequently prescribed for secondary prevention of vascular disease complications.[28] Revascularization is reserved for patients with chronic limb threatening ischemia or for select patients with a reduction in quality of life due to severe claudication. Open revascularization can entail bypassing the lower extremity arterial disease, locally removing the atheromatous plaque

(endarterectomy) or patching the artery to widen the lumen and thus allow for improved blood flow to the foot. Endovascular, or minimally invasive options use a combination of percutaneous arterial access, wires, balloons, and stents to either balloon-dilate or stent the arterial lumen open.

Endovascular Treatment

Percutaneous angioplasty and or stenting provides a minimally invasive opportunity to revascularize a threatened limb. This technique is favoured in patients who cannot tolerate open surgery or those with lesions that are amenable to endovascular treatment, such as short focal lesion. Patients who do not have an adequate saphenous vein for bypass may also undergo an attempted endovascular revascularization initially. Despite many limitations, the BASIL-1 (Bypass versus Angioplasty in Severe Ischemia of Limb) trial deduced that an "endovascular first" approach could be considered in patients with a life expectancy of less than two years to reduce patient morbidity and procedure cost.[29] However, the BEST-CLI (Best Endovascular versus Best Surgery in Chronic Limb-Threatening Ischemia) trial later countered that and showed that in patients with adequate saphenous vein and in whom both endovascular and open surgery were feasible, open bypass should be considered prior to endovascular attempts due to a reduction in major adverse limb and all-cause mortality rates.[30] Nevertheless, endovascular or hybrid-open and endovascular procedures remain viable frequently used options for revascularization in select patients.

Open Surgical Revascularization

There are multiple options for open surgical revascularization. These are generally tailored to the needs of the individual, taking into account patient presentation, fitness for open repair, anatomy of disease and availability of autologous conduit for bypass.

Femoral endarterectomy is a procedure in which the atheromatous plaque causing narrowing or obstruction of the femoral artery is removed. The common femoral artery is dissected in the groin and its branches are controlled. The artery is opened longitudinally and the intima with the atherosclerotic plaque is gently separated circumferentially from the underlying media. The atherosclerotic plaque is removed and the artery is repaired, usually with a patch (either from autologous vein, bovine pericardium or synthetic material) to ensure that the arterial lumen remains widely patent.

Open surgical bypass is another common procedure that involves bypassing a long obstructive atherosclerotic lesion by connecting a conduit to a patent segment of artery above and below the lesion, thus allowing blood to "bypass" the obstruction and perfuse the foot. A bypass conduit, either autologous vein or prosthetic material, is sewn into patent vessels proximally and distally to the lesion. The artery that the bypass is sewn into proximally must have sufficient blood inflow to perfuse the bypass and the distal artery to which the bypass is sewn must be continuous to the foot without flow-limiting lesions for the bypass to be successful. Common proximal targets in the limb are the femoral arteries and distal targets may be the above- or below knee popliteal artery, any of the tibial vessels, or the dorsalis pedis artery.

Amputation

When limb salvage is not possible, amputation is offered. Patients with extensive tissue loss, wet gangrene, those who are non-revascularizable with severe pain, patients unfit to undergo revascularization, and in some cases non-ambulatory patients may be offered this option. Minor amputation may involve one or more digits. Conversely, any amputation proximal to the ankle is defined as a major amputation. While fitting patients with a prosthesis following a

below-knee amputation is feasible, it is important to note that walking following this intervention requires significant cardiopulmonary requirements of the patient compared to ambulation on native limbs. The level of exertion of ambulation following an above knee amputation is even greater, and thus most vascular patients are unlikely to ambulate following this procedure.[31]

5.2.4 Complications following Lower Extremity Vascular Surgery

Perioperative morbidity is frequently seen post-revascularization, with estimates that approximately 35 to 50% of individuals experience at least one perioperative complication following open or endovascular revascularization.[32,33]

Open surgery often portends a greater risk of perioperative complications compared to endovascular surgery. These include early complications such as cardiopulmonary complications, bleeding, embolization or graft thrombosis, and surgical site infections or wound complications. The PREVENT III trial prospectively followed 1404 patients who underwent lower extremity bypass with vein graft enrolled at 84 institutions and found that 30-day mortality occurrent in 2.7% of patients, myocardial infarction in 4.7% and early graft occlusion in 5.2% of patients.[34]

Late complications following open repair can include late graft thrombosis, graft stenosis, aneurysmal degeneration, wound healing complications, graft infection, or persistent lymphedema.

In addition to cardiopulmonary and infectious complications, endovascular intervention-specific complications include access-site complications such as hemorrhage or pseudoaneurysm formation, arterial rupture, dissection, and distal embolization.

Surgical Site Infections and Poor Wound Healing

Surgical site infection is a common complication following lower extremity revascularization or major amputation, occurring in up to 30% of patients following lower extremity bypass.[35-37] Risk factors for surgical site infection include patient factors such as advanced age,[38] female sex,[39,40] obesity,[39,40] end stage renal disease on dialysis[39] and diabetes[40] as well as peri-procedure variables such as operative time,[39,41] hypothermia,[42] blood transfusion[41,42] or hyperglycemia.[40,43,44] Surgical site infections involving vascular graft or arterial involvement are classified according to the Szilagyi grade. This classification describes the severity of infection post open revascularization, ranging from cellulitis (Grade I) to graft infection (Grade III).[45]

Surgical site infections carry significant morbidity and have been shown to increase the risk of major adverse limb events such as graft occlusion and major amputation, increase the length of stay, and the risk of readmission.[39,46,47] Moreover, SSIs increase the risk of post-discharge institutionalization and loss of independence in a population that is comorbid and frail at baseline. SSIs also significantly increase the cost of care, not only due to higher rates of readmission, but because of the longitudinal outpatient antibiotic therapy and wound care required.[48]

5.2.5 Conclusion

Peripheral arterial disease is a major cause of disability in the elderly population. In addition to the risk of limb loss, patients are at high risk of developing cardiovascular and cerebrovascular disease. Treatment focuses on medical management of atherosclerotic risk

factors, lifestyle modification and surgical revascularization when necessary. Many options for revascularization exist including open, endovascular and hybrid options. Unfortunately PAD patients are at high risk for the development of post-operative complications given underlying comorbidities and frailty.

5.3 Perioperative Glycemic Control

5.3.1 Introduction

Hyperglycemia is defined as blood glucose equal to or greater than 10 mmol/L. This occurs in up to 30% of hospitalized patients and has been identified as a marker of surgical stress.[49,50] One major risk factor for perioperative hyperglycemia is diabetic status, however non-diabetic patients may also experience hyperglycemia in the perioperative period due to a post-surgical stress response. The percentage of non-diabetics experiencing stress-induced hyperglycemia increases with increased physiologic stress induced by the surgery, with up to 80% of non-diabetics experiencing a stress hyperglycemic response following coronary artery bypass surgery.[51-54] Physiologic perturbances in baseline glucose metabolism extend beyond the surgery and may linger for up to 30 days post procedure.[52,53]

Induction of hormones such as growth factor, cortisol, glucagon and epinephrine lead to hyperglycemia by inducing both gluconeogenesis and peripheral tissue insulin resistance.[55] While initially thought to be beneficial in critically ill patients, it has since been shown to cause endothelial dysfunction by reducing nitric oxide production and reduced ability for vasodilation.[56] An inflammatory reaction is provoked, as evidenced by increasing leukocyte and endothelial cell adhesion molecules combined with increased circulating cytokine levels such as tumour necrosis factor, IL-1ß and IL-8.[57] Interestingly, despite this upregulation of pro-

inflammatory cytokines, hyperglycemic patients are more susceptible to infection due to impaired neutrophil function in the hyperglycemic milieu.[56]

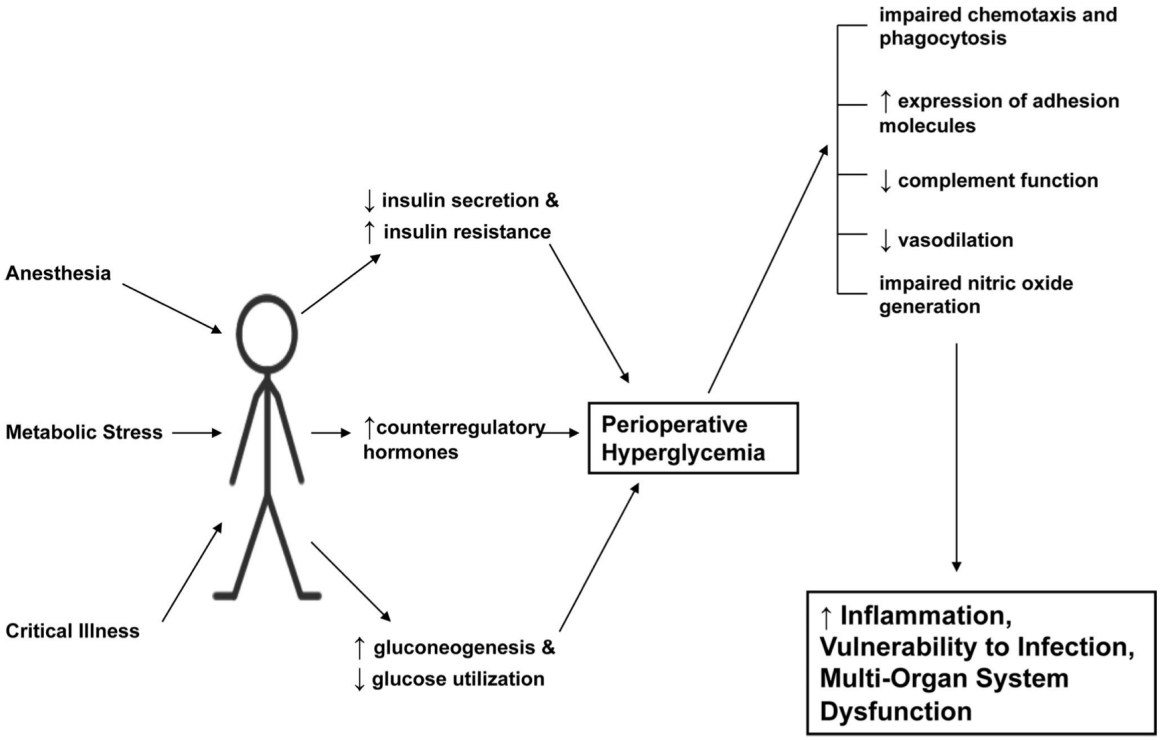

Figure 1. Pathophysiology of stress-induced hyperglycemia

Excerpted from Lipschutz et al., 2009 – permission obtained from publisher for use.[55]

On a macroscopic level these changes lead to a variety of negative outcomes for patients, with studies consistently showing perioperative hyperglycemia to be an independent risk factor for post-operative morbidity and mortality.[55] Patients experiencing hyperglycemia in the perioperative period experience greater risk of cardio-or cerebrovascular events.[53,54,58] Pro-inflammatory cytokines damage autologous tissue, cause organ injury and dysfunction, and may even contribute to increasing insulin resistance in tissues, exacerbating the problem.[55] Risk of

post-operative infection has been demonstrated to increase by 50 to 200% in the presence of hyperglycemia in a variety of surgical interventions.[53,58-61]

5.3.2 Intensive Insulin Therapy

In 2001 Van den Berghe et al published a randomized control trial of 1500 patients in the surgical intensive care unit who underwent intravenous insulin infusions to target a blood glucose range of 4 to 6 mmol/L rather than the standard target of 11.1 mmol/L.[62] Known as the first Leuven study, this team found that intensive insulin therapy was associated with a 34% decrease in mortality as well as decreased rates of sepsis and acute kidney failure.[62] This was followed by numerous studies in cardiac surgery demonstrating that the use of intensive insulin therapy during these procedures reduced the risk of mortality, surgical site infections, myocardial infarction as well as neurologic events.[63-69] As a result of these studies, glycemic control was added as a target following cardiac surgery, with the Society for Enhanced Recovery After Cardiac Surgery and Surgical Care Improvement projects both adding post-operative glycemic care to their expert recommendations.[70,71]

The efficacy and safety of intensive insulin therapy has however been challenged since Van den Berghe's first study. In 2006, the second Leuven study performed in critically ill medical patients failed to show any mortality benefit in medically ill patients undergoing intensive glycemic control and several studies were prematurely halted due to a high rate of severe hypoglycemic events.[72] Several studies also demonstrated conflicting evidence, with patients undergoing intensive insulin therapy experiencing either no benefit or even adverse events as a result of the therapy.[73] Lastly, there was concern regarding the widespread use of insulin itself, given the high potential for harm when misused or administered incorrectly.[55]

Further study is required to determine the safety and efficacy of intensive glycemic control following surgery. The challenges of intensive insulin therapy are widespread and the lack of uniformity across studies has made it difficult to compare results. Target patient populations, insulin doses and method of administration, frequency of blood glucose checks, blood glucose targets and ability to achieve these, and overall protocol design have added noise to the evaluation of this therapy. One systematic review of 16 studies on glycemic control found that the variation in protocols used, patient population, timing of protocol implementation and study methodology made it difficult to draw conclusions but that likely tight control to 8 mmol/L would be beneficial, with the possibility that tighter targets might be beneficial in a subset of patients, but that the specific characteristic of this population remains as of yet uncharacterized.[55]

5.3.3 Summary of Evidence

Perioperative hyperglycemia occurs as part of a surgical stress response invoking a combination of inflammatory cytokines and endothelial dysfunction which can lead to downstream organ damage and susceptibility to infection. Intensive insulin therapy performed in coronary artery bypass grafting patients revealed initial improvements in outcomes, however these findings were later refuted by studies performed in intensive care settings. Intensive insulin therapy may yet provide an excellent strategy for the control of surgery-induced hyperglycemia in a select patient population, however further prospective research is required to identify the most appropriate protocols as well as the most appropriate target population for this intervention.

6 Body of the Thesis

6.1 Introduction

The following manuscripts have been submitted for publication. As of the date of writing this, "Perioperative Glycemic Surveillance and Control – Current Practices, Efficacy and Impact on

Post-Operative Outcomes following Infra-inguinal Vascular Intervention" has been accepted for publication in the September 2023 issue of *Annals of Vascular Surgery*. The second manuscript has been submitted for consideration to *Annals of Vascular Surgery*.

The first manuscript presented as part of this thesis (Perioperative Glycemic Surveillance and Control – Current Practices, Efficacy and Impact on Post-Operative Outcomes following Infra-inguinal Vascular Intervention) sought to characterize baseline glycemic surveillance and interventions and their efficacy in patients undergoing open lower extremity vascular surgery at the McGill University Health Centre. In addition to describing current treatment patterns, the impact of hyperglycemia on post-surgical outcomes was assessed.

The second manuscript is a systematic review of the literature on the use of intensive insulin therapy in patients undergoing open lower extremity vascular surgery. The goal was to evaluate the pre-existing literature to establish whether evidence for the use of intensive insulin therapy in vascular surgery exists and what the impact of this treatment might have on a common post-operative complication – surgical site infections.

6.2 Manuscript #1 - Perioperative Glycemic Surveillance and Control – Current Practices, Efficacy and Impact on Post-Operative Outcomes following Infra-inguinal Vascular Intervention

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Abstract

Objectives: Perioperative glycemic control plays a pivotal role in improving post-surgical outcomes. Hyperglycemia occurs frequently in surgical patients and has been associated with higher rates of mortality and post-operative complications. However, no current guidelines exist regarding intra-operative glycemic monitoring of patients undergoing peripheral vascular procedures and post-operative surveillance is often restricted to diabetic patients. We sought to characterize the current practices around glycemic monitoring and efficacy of perioperative glycemic control at our institution. We also examined the impact of hyperglycemia in our surgical population.

Methods: This was a retrospective cohort study performed at the McGill University Health Centre and Jewish General Hospital in Montreal, Canada. Patients undergoing elective open lower extremity revascularization or major amputation between 2019-2022 were included. Data collected from the electronic medical record included standard demographics, clinical and surgical characteristics. Glycemic measurements and perioperative insulin use were recorded. Outcomes included 30-day mortality and post-operative complications.

Results: A total of 303 patients were included in the study. Overall, 38.9% of patients experienced perioperative hyperglycemia defined as glucose ≥ 180 mg/dl (10 mmol/L) during their hospital admission. Only twelve (3.9%) patients within the cohort underwent any intraoperative glycemic surveillance, while 141 patients (46.5%) had an insulin sliding scale prescribed post-operatively. Despite these efforts, 51 (16.8%) patients remained hyperglycemic for at least 40% of their measurements during their hospitalization. Hyperglycemia in our cohort

was significantly associated with an increased risk of 30-day acute kidney injury (11.9% vs. 5.4%, p = 0.042), major adverse cardiac events (16.1% vs. 8.6%, p = 0.048), major adverse limb events (13.6% vs. 6.5%, p = 0.038), any infection (30.5% vs. 20.5%, p = 0.049), intensive care unit admission (11% vs. 3.2%, p = 0.006) and re-intervention (22.9% vs 12.4%, p = 0.017) on univariate analysis. Furthermore, multivariable logistic regression including the covariates of age, sex, hypertension, smoking status, diabetic status, presence of chronic kidney disease, dialysis, Rutherford stage, coronary artery disease and perioperative hyperglycemia demonstrated a significant relationship between perioperative hyperglycemia and 30-day mortality (OR 25.00, 95% CI 2.469 – 250.00, p = 0.006), major adverse cardiac events (OR 2.08, 95% CI 1.008 - 4.292, p = 0.048), major adverse limb events (OR 2.24, 95% CI 1.020 – 4.950, p = 0.045), acute kidney injury (OR 7.58, 95% CI 3.021 – 19.231, p <0.001), reintervention (OR 2.06, 95% CI 1.117 - 3.802, p = 0.021) and intensive care unit admission (OR 3.38, 95% CI 1.225 – 9.345, p = 0.019).

Conclusion: Perioperative hyperglycemia was associated with 30-day mortality and complications in our study. Despite this, intra-operative glycemic surveillance occurred rarely in our cohort and current post-operative glycemic control protocols and management failed to achieve optimal control in a significant percentage of patients. Standardized glycemic monitoring and stricter control in the intra- and post-operative period therefore represent an area of opportunity for reducing patient mortality and complications following lower extremity vascular surgery.

Introduction

Hyperglycemia is a marker of physiologic stress commonly observed in the perioperative period.[74] Fasting prior to surgery, changes in medications, changes in baseline physical activity, inflammation and stress responses contribute to gluconeogenesis and insulin resistance.[75] The contemporary literature suggests that it may occur in up to 20-80% of patients depending on the type of surgery performed and the amount of physiologic stress induced by the procedure.[51,53,54,76] Furthermore, up to 30% of patients experiencing perioperative hyperglycemia are non-diabetic but experience "stress" hyperglycemia induced by their operation which can persist for up to 30 days post-operatively.[52,53]

There is mounting evidence that hyperglycemia in the perioperative setting has negative consequences for patients and contributes to poor outcomes following surgery.[75] Hyperglycemia in surgical patients has been associated with an increased risk of perioperative mortality and higher rates of perioperative morbidity, including higher rates of acute renal failure, cerebrovascular accidents, myocardial infarctions, wound complications, readmission and re-intervention.[53,54,58-60,77] Hyperglycemia in the 72 hours following vascular surgery has been associated with increased risk of short-term mortality, acute renal failure, surgical site infection, stroke and reintervention.[58]

Long-term glycemic control is essential to improve outcomes in vascular procedures, as poorly controlled hemoglobin A1c (HbA1c) has similarly been shown to negatively influence perioperative outcomes following vascular procedures. Unfortunately monitoring HbA1c is often suboptimal and many non-diabetic patients and up to 25% of diabetic patients will not have a recent HbA1c prior to undergoing lower extremity bypass.[78] Furthermore, pre-operative

glycemic control may be sub-optimal due to factors including a lack of healthcare resources, lack of support for patients or due to a precipitous need for the intervention[79,80] Optimal glycemic surveillance and control in the perioperative period therefore remains an independent potential target for reducing the risk of post-operative complications.

There is currently no widely-accepted consensus for perioperative glycemic monitoring in vascular patients.[81] Furthermore, guidelines sometimes provide differing targets and monitoring protocols that conflict and may be confusing. The American Diabetes Association suggests a general target blood glucose of 100-180 mg/dl (5.6-10 mmol/L) in non-critically ill diabetic patients pre-operatively and a post-operative target of 140 – 180 mg/dl (7.8 – 10 mmol/L). However, it also suggests that stricter targets of 100-180 mg/dl (5.6 – 10 mmol/L) or 110 – 140 mg/dl (6.1 – 7.8 mmol/L) may be more appropriate in select patients.[82] The Society for Ambulatory Anesthesia also suggests that diabetic patients, patients with a high pre-operative blood glucose or those who are undergoing surgery lasting longer than two hours should be carefully be monitored every 1-2 hours while undergoing their operation.[83,84] Unfortunately, nondiabetic patients are often excluded from practice guidelines, preventing identification and treatment of patients at risk of hyperglycemia in this population.

As a result, intra-operative surveillance is often poor, with studies demonstrating that up to 40% of diabetic patients may not undergo any intra-operative glycemic monitoring.[85] Furthermore, guidelines often ignore the increased insulin resistance that can occur in non-diabetic patients. We therefore sought to characterize the current practices around intra- and post-operative glycemic monitoring in patients undergoing lower extremity open vascular surgery, as well as

the efficacy of perioperative glycemic control at our institution. We also examined the impact of intra- and post-operative hyperglycemia on our surgical population.

Methods

Study Design

This multicentre retrospective cohort study consisted of all patients who underwent infra-inguinal revascularization or major amputations between 2019-2022 at the McGill University Health Centre and Jewish General Hospital between 2019-2020 in Montreal, Canada. Patients were selected based on procedural codes and electronic medical records (EMR) were used to determine eligibility based on the inclusion and exclusion criteria. Given the retrospective nature of the study, informed consent was not obtained. Ethics approval for the study was obtained from both the McGill University Health Centre and Jewish General Hospital research ethics boards.

Study Population

All patients who underwent open infra-inguinal revascularization or major limb amputation between January 2019 and November 2022 at the Royal Victoria Hospital and between January 2019 – December 2019 at the Jewish General Hospital were considered for inclusion in the study. Procedural codes were used to select patients for potential inclusion in the study. Patients were excluded from the study if they presented with an acute limb ischemia, traumatic injury, were admitted to the intensive care unit immediately prior to their operation or were less than 18 years of age at the time of the procedure.

Glycemic Measurements

Patient perioperative blood glucose values were obtained from point-of-care and arterial blood gas results recorded in the EMR at each site. Hyperglycemia was defined as blood glucose ≥ 180 mg/dl (10 mmol/L) and hypoglycemia was defined as blood glucose ≤ 72 mg/dl (4.0 mmol/L). Glycemic values were defined as being within range if they were between 72 – 180 md/dl (4 – 10 mmol/L). Pre-, intra- and post-operative glycemic values were collected from the EMR and anesthetic record. Use of intra- and post-operative insulin was determined based on the anesthetic record and post-operative orders.

Data Collection

Data collection was performed using the EMR and was entered into a secure REDCap database (Vanderbilt University). Patient demographics, baseline comorbidities, clinical characteristics and severity of pre-existing vascular disease were collected, as were procedural data and post-operative outcomes. Pre-, intra- and post-operative glycemic measurements were also recorded.

Major adverse cardiac events (MACE) were defined as the occurrence of myocardial infarction, acute coronary syndrome, stroke or heart failure during admission. Major adverse limb events (MALE) were defined as severe ischemia of the affected limb leading to intervention or major amputation. Wound complications were defined as a composite of surgical site infection, dehiscence or lymphocele development at the surgical incision.

Statistical Analysis

Our primary goal was to characterize the use and efficacy of current glycemic surveillance and treatment practices. Secondary endpoints included 30-day mortality and complications including major adverse cardiac events (MACE), major adverse limb events (MALE), need for

reintervention, acute kidney injury, wound complications, need for readmission and length of stay.

Statistics were performed using the SPSS statistical software v. 29.0 (IBM Corporation, Armonk, NY). On univariate analysis, continuous variables were analysed using a student's t-test if normally distributed or by Mann-Whitney U test if they did not have a normal distribution. Categorical variables were analyzed using Fischer's exact test or chi square test as appropriate. Multinomial logistic regression was used to assess the risk of 30-day complications, using the covariates of age, sex, perioperative hyperglycemia, and any baseline characteristics with a p-value of less than 0.10 when compared on univariate analysis. P-values of ≤ 0.05 and confidence intervals of 95% were considered significant.

Results

A total of 303 patients were included in the study. The average age was 71 years and 218 (69.0%) of patients were male. Two hundred and fifty-seven (84.8%) patients had a pre-existing diagnosis of peripheral arterial disease (PAD). Patients largely underwent vascular intervention for chronic limb-threatening ischemia (N = 281, 92.1%), however 22 patients (7.3%) underwent procedures for non-atherosclerotic vascular disease (Table 1).

Parameter	Total (N = 303)	Glucose > 180 mg/dl (N = 118)	Glucose < 180 mg/dl (N = 185)	P-value
Age, years	70.6 ± 10.43	70.8 ± 9.63	71.5 ± 10.97	0.409
Sex				
Female	85 (26.9)	33 (27.9)	52 (28.1)	

Male	218 (69.0)	85 (63.9)	133 (71.9)	0.979
Mean BMI kg/m2	26.1 ± 5.11	26.5 ± 5.0	25.9 ± 5.18	0.187
Diabetes				
Yes	133 (43.9)	99 (83.9)	34 (18.4)	
No	170 (56.1)	19 (16.1)	151 (81.6)	< 0.001
Smoking History				
Yes	243 (79.9)	88 (74.6)	155 (83.8)	
No	60 (19.8)	30 (25.4)	30 (16.2)	0.05
HTN				
Yes	253 (83.5)	110 (93.2)	143 (77.3)	
No	50 (16.5)	8 (6.8)	42 (22.7)	< 0.001
COPD				
Yes	78 (25.7)	30 (25.4)	48 (25.9)	
No	225 (74.3)	88 (74.6)	137 (74.1)	0.919
CAD				
Yes	141 (46.5)	64 (54.2)	77 (41.6)	
No	162 (53.5)	54 (45.8)	108 (58.4)	0.032
CKD				
Yes	57 (18.8)	33 (27.9)	24 (13.0)	
No	246 (81.2)	85 (63.9)	161 (87.0)	0.001
ESRD				
Yes	9 (9.7)	6 (5.1)	3 (1.6)	
No	294 (90.3)	112 (94.9)	182 (98.4)	0.096
PAD				
Yes	257 (84.8)	103 (87.2)	154 (83.2)	
No	46 (15.2)	15 (12.7)	31 (16.8)	0.412
Rutherford				
0	22 (7.3)	5 (4.2)	17 (9.2)	
I - III	67 (22.1)	11 (9.3)	56 (30.3)	
IV - VI	214 (70.6)	102 (86.4)	112 (60.5)	< 0.001
ABI	0.53 ± 0.27	0.5 ± 0.26	0.55 ± 0.27	0.094
TP	27.1 ± 35.7	20.9 ± 28.5	31.3 ± 41.2	0.238

BMI – Body Mass Index; COPD – Chronic Obstructive Pulmonary Disease; CAD – Coronary Artery Disease; CKD – Chronic Kidney Disease; PAD – Peripheral Arterial Disease; ABI – Ankle Brachial Index; TP – Toe Pressure

Table 1. Baseline characteristics of total cohort as well as hyperglycemic and normoglycemic groups.

One hundred and eighteen (38.9 %) patients experienced hyperglycemia > 180 mg/dl (> 10 mmol/L) post-operatively (Table 1). Patients who experienced hyperglycemia were more likely to be diabetic (83.9% vs. 18.4%, $p < 0.001$), hypertensive (93.2% vs. 77.3%, $p < 0.001$), have coronary artery disease (CAD) (54.2% vs. 41.6%, $p = 0.032$), chronic kidney disease (CKD) (27.9% vs. 13.0%, $p = 0.001$) and present with Rutherford grades IV to VI (86.4% vs. 60.5%, $p < 0.001$).

Despite pre-existing guidelines, only 12 patients (3.9%) patients underwent intra-operative glucose measurements, of which seven (58.3%) were diabetic. Intra-operative insulin (either subcutaneous or intravenous) was utilized in 18 (6.0%) patients (Table 2). Post-operative insulin sliding scale was prescribed in 141 (46.5%) patients and the Endocrinology service was consulted for post-operative glycemic management assistance for 22 (7.3%) patients (Table 2). Interestingly, only 65 patients (21.4%) underwent a pre-operative HbA1c measurement (Table 2).

Parameter	Total (N = 303)	Glucose > 180 mg/dl (N = 118)	Glucose < 180 mg/dl (N = 185)	P-value
Pre-Operative Glucose (md/dl; mmol/L)	122.4 ± 44.1 (6.8 ± 2.45)	151.2 ± 52.0 (8.4 ± 2.89)	104.4 ± 25.0 (5.8 ± 1.39)	< 0.001
HbA1c (%)*	7.2 ± 1.72	7.7 ± 1.9	6.3 ± 0.99	0.004
Intra-operative Glucose Measurements				

Yes	12 (3.9)	4 (3.4)	8 (4.3)	
No	291 (95.9)	114 (96.6)	177 (95.7)	0.639
Intra-operative Insulin				
Yes	18 (6.0)	15 (12.7)	3 (1.6)	
No	285 (94.0)	103 (87.3)	182 (98.4)	< 0.001
Post-Operative Sliding Scale Prescribed				
Yes	141 (46.5)	99 (83.9)	42 (22.7)	
No	162 (53.4)	19 (16.1)	143 (77.3)	< 0.001
Endocrinology Consult				
Yes	22 (7.3)	22 (11.9)	0 (0.0)	
No	281 (92.7)	96 (90.1)	185 (100.0)	< 0.001
Maximum Glucose Attained during admission (mg/dl; mmol/L)	232.2 ± 106.2 (12.9 ± 5.9)	284.4 ± 84.4 (15.8 ± 4.69)	129.6 ± 26.3 (7.2 ± 1.46)	< 0.001
Percentage of Glucose Measurements in Target Range	85.1 ± 23.52	63.1 ± 24.93	98.9 ± 3.89	< 0.001

**Up-to-date pre-operative HbA1c available for 65 patients (21.5% of total cohort)*

Table 2. Pre-, intra- and post-operative glycemic measurements and control for total cohort and separated into hyperglycemic and normoglycemic groups.

Patients who experienced intra- or post-operative hyperglycemia were more likely to present with a higher pre-operative random glucose (8.4 vs. 5.8 mmol/L, $p < 0.001$), receive intra-operative insulin (12.7% vs. 1.6%, $p < 0.001$), have a post-operative sliding scale prescribed (83.9% vs. 22.7%, $p < 0.001$) and require endocrinologist consultation during their admission (11.9% vs. 0%, $p < 0.001$). Despite these measures, patients with at least one

hyperglycemic value during their post-operative course spent significantly less of their admission in the normoglycemic range (62.9% of measurements in glycemic target range vs. 98.9%, $p < 0.001$) (Table 2).

Thirty-day post-operative complications were analysed using univariate analysis. Patients who experienced hyperglycemia during their admission were more likely to experience 30-day acute kidney injury (11.9% vs. 5.4%, $p = 0.042$), MACE (16.1% vs. 8.6%, $p = 0.048$), MALE (13.6% vs. 6.5%, $p = 0.038$), any infection (30.5% vs. 20.5%, $p = 0.049$), intensive care unit (ICU)-admission (11% vs. 3.2%, $p = 0.006$) and re-intervention (22.9% vs 12.4%, $p = 0.017$) (Table 3). Hyperglycemic patients were also significantly more likely to experience a longer length of stay (12.5 vs. 6.5 days, $p < 0.001$). While non-significant, mortality also trended upwards in patients who experienced at least one episode of perioperative hyperglycemia (3.4% vs. 0.5%, $p = 0.077$) (Table 3).

Parameter	Total (N = 303)	Glucose > 180 mg/dl (N = 118)	Glucose < 180 mg/dl (N = 185)	P-value
Mortality	5 (1.6)	4 (3.4)	1 (0.5)	0.077
Acute Kidney Injury	24 (7.9)	14 (11.9)	10 (5.4)	0.042
MACE	35 (11.6)	19 (16.1)	16 (8.6)	0.048
MALE	28 (9.2%)	16 (13.6)	12 (6.5)	0.038
Any Infection	74 (24.4)	36 (30.5)	38 (20.5)	0.049
Wound Complication	67 (22.1)	23 (19.5)	44 (23.8)	0.38
Surgical Site Infection	45 (14.9)	17 (14.4)	28 (15.1)	0.862
Wound Dehiscence	32 (10.6)	22 (18.6)	10 (5.4)	0.345
Reintervention	50 (16.5)	27 (22.9)	23 (12.4)	0.017

Return to ER	40 (13.2)	10 (8.5)	30 (16.2)	0.052
Readmission	23 (7.6)	8 (6.8)	15 (8.1)	0.67
Length of Stay	8.6 ± 17.71	12.5 ± 18.15	6.2 ± 17.07	< 0.001
ICU Admission	19 (6.3)	13 (11.0)	6 (3.2)	0.006
MACE – Major Adverse Cardiac Events (myocardial infarction, acute coronary syndrome, stroke, heart failure); MALE – Major Adverse Limb Events (severe ischemia leading to intervention or major amputation); ER – Emergency Room; ICU – Intensive Care Unit				

Table 3. Univariate analysis of 30-day post-operative complications.

Multivariable logistic regression was used to control for confounding baseline variables and assess the risk of 30-day complications (Table 4). The covariates of age, sex, hypertension, smoking status, diabetes, coronary artery disease, chronic kidney disease, dialysis, Rutherford stage IV-VI and occurrence of hyperglycemia were included in the multivariable analysis. Following these analyses, perioperative hyperglycemia was found to significantly increase the odds of 30-day mortality (OR 25.00, 95% CI 2.469 – 250.00, p = 0.006), major adverse cardiac events (OR 2.08, 95% CI 1.008 - 4.292, p = 0.048), major adverse limb events (OR 2.24, 95% CI 1.020 – 4.950, p = 0.045), acute kidney injury (OR 7.58, 95% CI 3.021 – 19.231, p <0.001), reintervention (OR 2.06, 95% CI 1.117 - 3.802, p = 0.021) and intensive care unit admission (OR 3.38, 95% CI 1.225 – 9.345, p = 0.019).

Parameter	OR (95% CI)	P-Value
Mortality	25.00 (2.469 – 250.00)	0.006
Acute Kidney Injury	7.58 (3.021 – 19.231)	<0.001
MACE	2.08 (1.008 - 4.292)	0.048
MALE	2.24 (1.020 – 4.950)	0.045
Any Infection	1.69 (0.982 - 2.841)	0.058
Reintervention	2.06 (1.117 - 3.802)	0.021
Surgical Site Infection	0.93 (0.484 – 1.792)	0.832

Wound Complication	0.83 (0.472 – 1.456)	0.513
ICU Stay	3.38 (1.225 – 9.345)	0.019
Readmission	0.81 (0.333 – 1.984)	0.648
MACE – Major Adverse Cardiac Events (myocardial infarction, acute coronary syndrome, stroke, heart failure); MALE – Major Adverse Limb Events (severe ischemia leading to intervention or major amputation); ICU – Intensive Care Unit		

Table 4. Multivariable analysis of association between perioperative hyperglycemia and 30-day complication rates incorporating covariates of age, sex, presence of hyperglycemia, hypertension, CAD, CKD, dialysis, diabetes, smoking status and Rutherford stage IV-VI.

Discussion

Despite the well-described harm caused by perioperative hyperglycemia, our study highlights a lack of consistency in the glycemic management and surveillance of patients undergoing vascular surgery. Given the lack of clinical guidelines and conformity, intra-operative glycemic surveillance in our institution was low, with only 3.9% of patients undergoing a single blood glucose check during their operation. Furthermore, this occurred despite the presence of a large diabetic cohort (43.9%) within the study group, the presence of pre-operative hyperglycemia > 180 mg/dl (10 mmol/L) within 12.2% of the population and an average operative time of 159 minutes, all of which remain relative indications for hourly surveillance and intra-operative glycemic control using insulin.[84]

Despite the use of adjuncts such as the use of our institutional post-operative insulin sliding scale targeting a blood glucose of < 180 mg/dl (10.0 mmol/L), 61.1% of patients experienced at least one hyperglycemic value during their admission, with 16.8% remaining within the target glycemic range of 72 – 118 mg/dl (4-10 mmol/L) for only 40% of their glucose

measurements. Of the cohort that experienced perioperative hyperglycemia, 16.1% of patients were non-diabetic, indicating that they might be experiencing "stress" hyperglycemia and transient insulin resistance following the physiologic stress of their respective procedures.[52] This is consistent with pre-existing research demonstrating a 20-30% rate of non-diabetic patients who experience transient post-operative glycemic elevation following non-cardiac surgery.[53]

Our study echoed many predecessors in describing the poor outcomes associated with perioperative hyperglycemia. Multivariable regression controlling for confounders demonstrated a significant relationship between perioperative hyperglycemia and 30-day mortality, acute kidney injury, MACE, MALE, reintervention and admission to the ICU. Furthermore, while the presence of diabetes and elevated HbA1c have previously been demonstrated to increase the incidence of MALE, our study demonstrates that even when controlling for the presence of diabetes, perioperative hyperglycemia is independently associated with MALE.[80] Unfortunately a majority of patients in our cohort did not have a pre-operative HbA1c and so this population was not included in further analyses. Nevertheless, these findings demonstrate that improvements in current perioperative glycemic monitoring and treatment paradigms are necessary.

Glycemic control should ideally begin far in advance of planned surgical care, however due to system and patient constraints this is often not achieved upon presentation for surgery. In our own cohort, hemoglobin A1c was performed in only a minority of the cohort and remains a target for improvement. On admission however, it is possible that in the perioperative period at least, glycemic control remains an underutilized tool for improving post-surgical outcomes following open lower extremity revascularization or major amputation. Unfortunately the poor efficacy of the traditional insulin sliding scale is also well-documented, with studies

demonstrating that it may fail to prevent hyperglycemia in up to 98% of admitted patients.[86] Conversely, Ehrenfeld et al. demonstrated that within a diabetic cohort, glycemic surveillance could be improved from 60 to 80% simply by instituting an intra-operative protocol with the ability to remind physicians to repeat glucose measurements. This maneuver alone improved glycemic control and resulted in a significant reduction in surgical site infection rates.[85] The implementation of surveillance protocols, or more recently the use of continuous blood glucose monitoring intra-operatively could therefore provide a straight-forward solution that could have a significant impact on patient outcomes simply by improving physician awareness of out-of-range glucose measurements. In addition, both intra- and post-operative glycemic monitoring should be considered for all patients undergoing vascular procedures regardless of diabetic status to allow for identification and appropriate care of patients who experiencing "stress" hyperglycemia.

Despite available adjuncts, 38.9% of patients experienced hyperglycemia during their hospital stay, indicating that the current glycemic control paradigm at our institution is not sufficient. Adjuncts such as intra-operative glycemic insulin administration, pre-operative carbohydrate loading and post-operative resumption of oral hypoglycemic agents and metformin have been shown to improve patient outcomes by modulating insulin resistance and glucose metabolism.[63,87-89] Stricter glycemic targets for both the intra- and post-operative period have also been shown to be beneficial in select non-critically ill surgical patients, although variability exists within the literature depending on type of procedure performed and protocol used.[90-92] This remains an under-studied topic in vascular surgery and will benefit from future research.

This study has several limitations. It is retrospective in nature and therefore subject to bias. Given the single-centre multi-hospital design its results may not be applicable to other

institutions. Most patients included in the study were male, thus our results may not apply to women. It does not account for intra-operative measurements which are not documented within the EMR or on the anesthetic record and may therefore underestimate the number of glycemic measurements which were performed. Post-operative glycemic management was not uniform and may include any combination of oral hypoglycemics, the standard hospital insulin sliding scale or a modified sliding scale with baseline insulin provided. Lastly, confounding remains a risk when assessing our post-operative outcomes, although we attempted to control for these in our multivariable analysis.

Conclusion

Perioperative hyperglycemia was a frequent occurrence in our study, regardless of diabetic diagnosis. Despite this, intra-operative glycemic surveillance occurred rarely in our cohort and failed to meet the standards of existing guidelines for intra- and post-operative glycemic control. Standard post-operative glycemic control protocols and management also failed to achieve optimal post-operative control in a significant percentage of patients. Furthermore, perioperative hyperglycemia was significantly associated with 30-day mortality and a variety of post-operative complications. Standardized glycemic monitoring and stricter control in the intra- and post-operative period therefore represent an area of opportunity for reducing patient mortality and complications following lower extremity vascular surgery.

6.3 Bridging Text

The previous manuscript revealed deficiencies both in intra-operative surveillance as well as intra- and post-operative glycemic control of patients undergoing open infrainguinal vascular

surgery within the McGill network. Furthermore, as previously reported we also established that perioperative hyperglycemia was independently associated with significant morbidity and mortality within our population. These findings established the need for improvements in both perioperative glycemic surveillance and control in our patient population.

Given the benefits of intensive insulin therapy identified in cardiac surgery patients,[62,63,66-69] we deduced that this intervention might similarly benefit vascular surgery patients and improve perioperative outcomes. We therefore sought to evaluate the literature for similar studies performing intensive insulin therapy in the setting of open lower extremity vascular surgery. Despite not having found an increased rate of surgical site infections in the hyperglycemic cohort of our retrospective study, we were interested in the literature for this outcome given the large amount of evidence for intensive insulin therapy reducing the risk of surgical site infections by 50 to 70% in the post-cardiac surgery population.[62,63] Furthermore, surgical site infections occur frequently following lower extremity intervention and place a significant burden on the patient as well as on the healthcare system.[55] Our primary outcome was to evaluate papers which reported surgical site infection as an outcome following intervention. The following manuscript details our search of the literature and highlights the lack of studies available on the use of intensive insulin therapy in the peripheral arterial disease population. Given the paucity of studies the following studies were evaluated as a systematic review rather than as a meta-analysis. The review emphasizes the need for further prospective studies on the use of strict glycemic control in this population.

6.4 Manuscript # 2 – A scoping review on the impact of strict perioperative glycemic control on surgical site infections following lower extremity vascular surgery

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Abstract

Objective: To evaluate the impact of strict perioperative glycemic control intervention in patients undergoing open lower extremity vascular surgery on surgical wound complications.

Methods: A scoping review was performed using the following databases: MEDLINE, EMBASE, CINAHL, Web of Science, Cochrane Library, and ClinicalTrials.gov from inception until November 2021. Studies were included if they described patients undergoing surgical lower extremity vascular reconstruction, if patients received a perioperative intervention for glucose control, and if they reported on surgical wound complication and morbidity outcomes. Study characteristics and count data on demographic variables, medical comorbidities, and primary outcomes were reported in a narrative fashion. Risk of bias was assessed with the Cochrane ROBINS-I tool.

Results: The search strategy yielded 8,354 articles which were assessed by title and abstract by two independent reviewers. Two studies that met eligibility criteria were included in the review. Both studies were prospective non-randomized trials, with one study (n=1, 50%) utilizing historical controls and the other study being a single-arm intervention (n=1, 50%). Both studies (n=2, 100%) utilized an intravenous insulin protocol to target a finger stick blood glucose level of 80-150 mg/dl. Only one study (n=1, 50%) reported a significant reduction in surgical site infection following the insulin infusion protocol compared to controls (4% vs. 11%, p=0.047), particularly in diabetic patients. The other (n=1, 50%) did not report a reduction in surgical site infections. Risk of bias was considered moderate for one study (n=1, 50%) and serious for the other study (n=1, 50%).

Conclusion: Despite evidence demonstrating a strong relationship between perioperative hyperglycemia and surgical site infections, perioperative glycemic control remains poorly studied within vascular surgery. Existing studies are underpowered and do not achieve reliable glucose control in the target range. As the current literature on this topic is largely characterized by observational data, prospective, interventional data on perioperative glucose control is required to determine the effect that this could have on surgical site infection rates.

Introduction

Hyperglycemia is marker of physiologic stress commonly observed in post-operative patients.[74] Fasting prior to surgery, changes in medications, changes in baseline physical activity, inflammation and stress responses contribute to gluconeogenesis and insulin resistance. Regardless of diabetic status, there is a plethora of evidence that hyperglycemia in the perioperative setting has negative consequences for patients. Hyperglycemia in surgical patients has been associated with an increased risk of perioperative mortality and higher rates of perioperative morbidity, including higher rates of acute renal failure, cerebrovascular accidents, myocardial infarctions, wound complications, readmission and re-intervention. [53,54,58-60,77] In the vascular surgery population, acute hyperglycemia in the 72h following surgery has been associated with increased risk of short-term mortality, acute renal failure, surgical site infection, stroke and reintervention.[58] While the current accepted upper target for glycemia is 180 mg/dl (8.3 mmol/L), one study on patients undergoing coronary bypass demonstrated that any 18 mg/dl (1 mmol/L) rise in glucose above 110 (6.1 mmol/L) mg/dl in the perioperative period can increased the risk of adverse events by 17%.[93]

The negative outcomes on even a small rise in perioperative glucose levels have been most extensively described in the cardiac surgery literature and have changed the standard of care for patients undergoing cardiac procedures. The Leuven Surgical Trial, conducted in a randomized, prospective fashion on 1548 post-surgical patients in the intensive care unit, demonstrated a beneficial effect of strict glycemic control on post-operative outcomes, including mortality.[62] Based in part on this research, the Society for Thoracic Surgeons Practice Guidelines on blood glucose management during cardiac surgery recommend intra-operative intravenous insulin infusions for diabetic or persistently hyperglycemic patients undergoing cardiac surgery.[94]

However, despite relatively high post-operative wound infection rates and clear evidence in the vascular surgical literature linking pre- and perioperative hyperglycemia to surgical site infections, there have been few studies examining the effect of perioperative glycemic control on post-operative outcomes such as surgical site infections following peripheral vascular intervention. Given the multiple comorbidities of vascular surgery patients and their predilection to developing postoperative wound infections, implementation of intensive insulin therapy perioperatively may alter risks for adverse outcomes. Therefore, the aim of this review is to identify the effects of perioperative intensive insulin interventions on post-operative complications, such as surgical wound complications in patients undergoing lower extremity vascular reconstruction.

Methods

A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard guidelines.[95] This review is registered with the International Prospective Register of Systematic Reviews (CRD42021289266).

Eligibility Criteria

Studies that met the following criteria were included in the review: (1) studies published in the English language; (2) patients undergoing open infrainguinal revascularization (ie. reconstruction requiring surgical incision) for peripheral arterial disease; (3) use of an intensive glucose control protocol during the perioperative period (defined as upper target limit of <180 mg/dl); (4) reported on any of the outcomes of interest (primary outcome: 30-day surgical wound complications, secondary outcomes: perioperative complications). Studies were excluded from

the review if they (1) were not published in English; (2) did not implement a perioperative (defined as the period from patient admission for the surgical procedure of interest to discharge from hospital) glucose control intervention; (3) pooled outcomes with various unrelated surgeries (e.g. studies which pooled lower extremity revascularization and abdominal aortic aneurysm repair); (4) did not report on the primary or secondary outcomes of interest; and (5) were considered as a letter to the editor, conference abstract, systematic review, or narrative review.

Literature Search Strategy

The search strategy was applied to the following databases on November 15th, 2021: MEDLINE (1946 – November 15th, 2021), EMBASE (1947 – November 15th, 2021), Web of Science (1806 – November 15th, 2021), CINAHL (1937 – November 15th, 2021), Cochrane Library (1996 – November 15th, 2021), and *ClinicalTrials.gov*. All databases were searched from inception and there were no date limits or filters applied to the search strategy. MeSH terms and keywords were adapted to each database. The search strategy can be found in Supplemental Table 1.

Citations from each database were imported into EndNote X9 Software (Clarivate, Philadelphia, PA, USA) for duplicate detection. Flagged duplicates were manually reviewed prior to removal. After duplicate detection, the remaining citations were exported from EndNote X9 to the Rayyan QCRI online software (Rayyan Systems Inc., Qatar)[96] to be screened by title and abstract in accordance with the predetermined eligibility criteria.

Study Selection

All titles and abstracts were screened independently by two authors (A.E.K. and J.G.A.) and conflicts were resolved after a discussion with a third author (A.A.N). Studies were then evaluated with a full-text read by two authors (A.E.K. and J.G.A.) using the outlined eligibility criteria. Reasons for conflicts between the two authors were documented and resolved with discussion. Conflicts that arose were resolved with discussion and a third author (A.A.N) was consulted for a final decision.

The reference lists of studies that met inclusion criteria were searched by title and studies that were not already found in the original search strategy were assessed with a full-text read. Reasons for inclusion or exclusion of an article during the full-text phase were documented.

Data Collection

Two authors (A.E.K. and J.G.A.) created a data extraction sheet using Microsoft Excel (Microsoft Corporation, Redwood, Washington, USA) based on the agreed upon variables of interest. These same two authors independently extracted data and entered crude data into the pre-determined data sheet.

Data included study characteristics, description of the glucose controls protocol used, patient demographic information, medical comorbidities and medications, description of peripheral vascular disease, primary and secondary outcomes of interest.

Data Synthesis and Quality Assessment

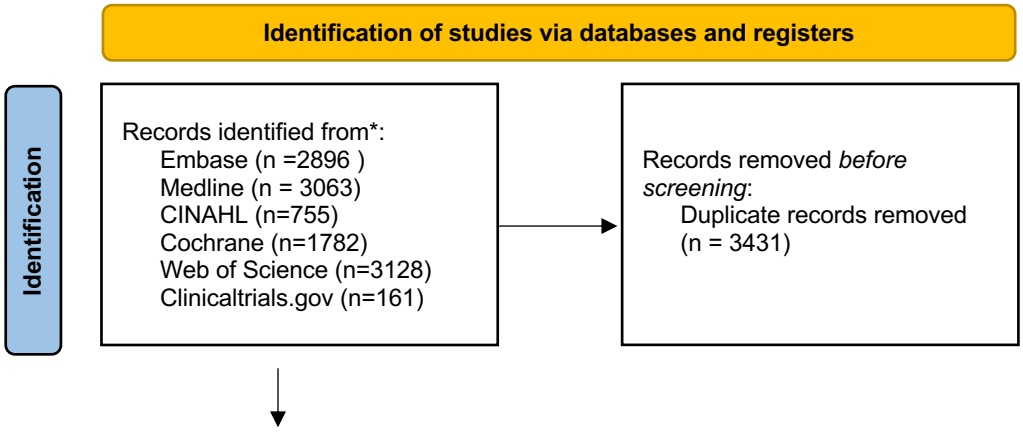
Given the small number of studies eligible following the selection process, a meta-analysis of primary or secondary outcomes to investigate the effect of a glucose control intervention was not conducted. However, a narrative synthesis of quantitative data[97] regarding

study characteristics, patient demographics, and outcomes of interest was conducted to identify reporting patterns in perioperative glucose control trials.

Quality assessment of included studies was independently conducted by two authors (A.E.K. and J.G.A.) with a third author (A.A.N.) serving as adjudicator. Methodological quality was evaluated using the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool for non-randomized interventional studies.[98,99] The ROBINS-I tool was used to describe the overall risk of bias of individual studies based on domains examining potential confounders, selection of participants, information bias, outcome measurement bias, and reporting bias.[99]

Results

The search strategy initially yielded 11.785 articles. Following duplicate detection and review, 3,431 articles were removed and 8,354 were screened by title and abstract. Seven articles were included in the full-text review and ultimately two studies[100,101] met the pre-determined eligibility criteria. No additional articles were found through a citation search in the 7 articles assessed with a full-text read. Figure 1 details the PRISMA flow diagram and Supplemental Table 2 details articles that were excluded during the full-text review with justification.



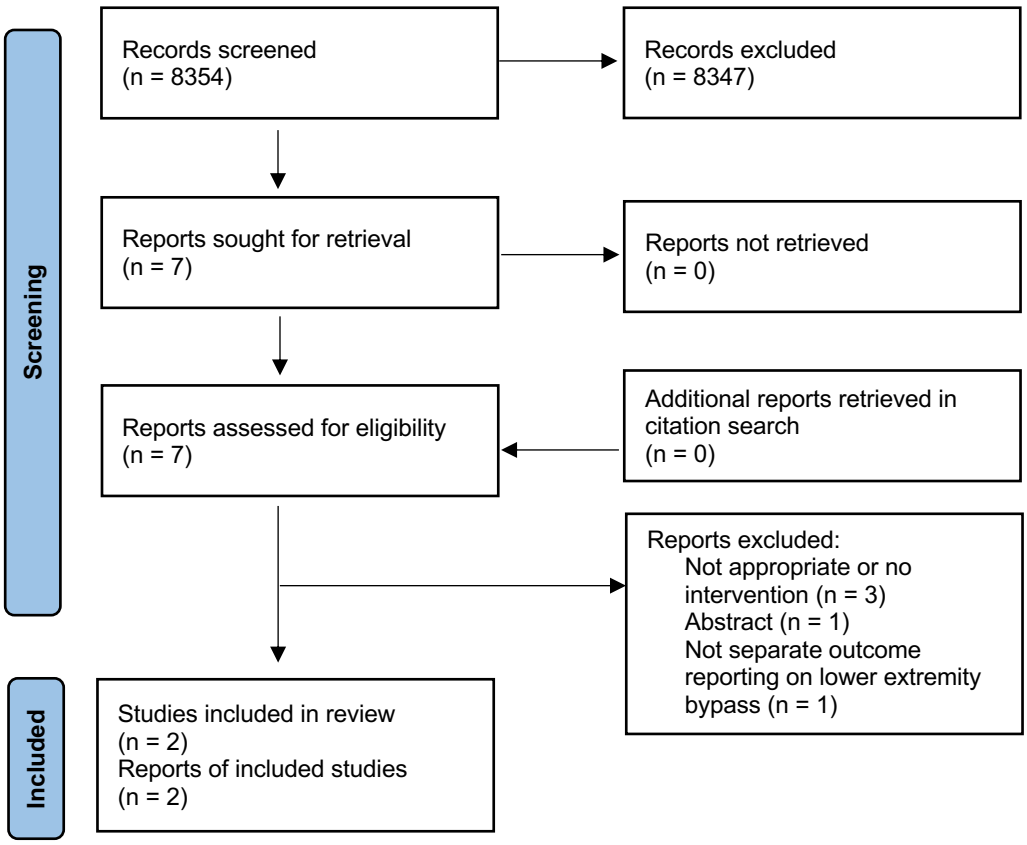


Figure 1. PRISMA Flow Diagram outlining the search strategy.

Quality Assessment

The ROBINS-I tool was applied to the two eligible studies (Hirashima et al. and Steely et al.). One study (Hirashima et al., n=1/2, 50%)[100] was deemed to have moderate risk of bias and the other (Steely et al., n=1/2, 50%)[16] was evaluated to have a serious risk of bias (Figure 2).

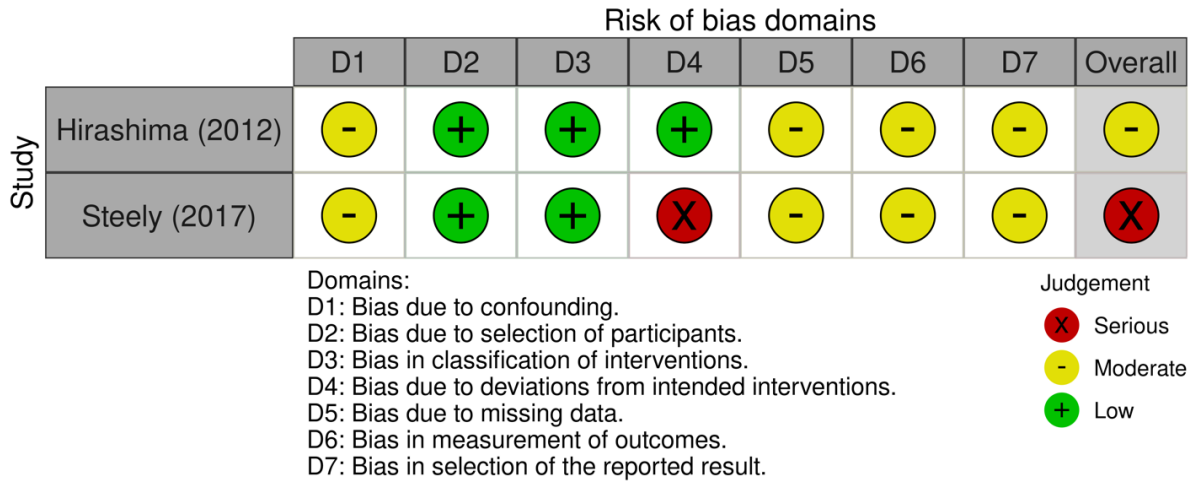


Figure 2. Risk of bias as determined by the ROBINS-I tool. The ROBINS-I tool evaluates methodological quality based on seven domains of bias. Study bias may be evaluated as low risk, moderate risk, serious risk, or critical risk.

Study Characteristics

Both studies (n=2, 100%) were conducted within the United States and were prospective non-randomized trials of glucose control interventions in lower extremity bypass surgeries.[100,101] One study (Hirashima et al., n=1, 50%)[100] compared the glucose intervention group to historical controls, while Steely et al. involved a single-arm glucose-management intervention without comparing to a control group (n=1, 50%).[101]

Regarding the glucose control interventions that were implemented, both studies (n=2, 100%)[100,101] initiated a postoperative intravenous insulin protocol (lasting 72 hours) to target a finger stick blood glucose range of 80-150 mg/dl. One study (Steely et al., n=1, 50%)[101] reported that patients were placed on a subcutaneous insulin protocol after the 72 hour postoperative

period while the Hirashima et al. (n=1, 50%)[100] provided a detailed overview of protocols in the event of hyperglycemia or hypoglycemia.

Demographics and Medical Comorbidities

A total of 206 patients were identified across the two studies with 157 patients undergoing a glycemic control intervention. Most patients receiving an intervention were male (n=126, 80.3%) and had a history of smoking (n=147, 93.6%, Supplemental Table 3).

Frequently reported medical comorbidities amongst patients undergoing glycemic control included diabetes (n=71, 45.2%), dyslipidemia (n=125, 79.6%), hypertension (n=129, 82.2%), congestive heart failure (n=6, 3.8%), chronic obstructive pulmonary disease (n=24, 15.3%), and end stage renal disease/renal failure (n=9, 5.7%, Supplemental Table 4). Additionally, 36.9% (n=58) had previously undergone a surgical or percutaneous cardiac intervention.

Concomitant medication use was only consistently reported in Hirashima et al. (n=1, 50%).[100] However, preoperative insulin use was reported in 25.5% (n=40/157) of patients undergoing lower extremity revascularization.

Indications for surgical intervention amongst patients enrolled in a glucose control protocol included claudication (n=52, 33.1%) and chronic limb threatening ischemia (n=89, 56.7%). However Hirashima et al. (n=1, 50%)[100] reported on patients receiving surgical intervention for asymptomatic peripheral arterial disease and acute limb ischemia. Venous grafts were used in 76.4% (n=120/157) of patients whereas prosthetic grafts were used in 22.9% (n=36/157) of patients (Supplemental Table 5).

Outcomes

As only two studies were included in this review, a meta-analysis on primary or secondary outcomes was not performed.

The primary outcome of overall surgical wound complications was reported in both studies, with a total of 18 wound complications amongst intervention recipients when pooling patients from who did not undergo intensive insulin therapy in either study (9.5%). [100] Hirashima et al. reported a significant reduction in surgical site infection following the insulin infusion protocol compared to controls (4% vs. 11%, p=0.047, as reported by the study), however when further stratifying for diabetes, this reduction in wound complications was only significant in diabetic patients (0% vs 10%, p=0.03, as reported by Hirashima et al.). While there was also a trend towards reduced number of surgical site infections in non-diabetic patients undergoing glucose management (7% vs. 12%, p=0.42, as reported by Hirashima et al.), this did not reach significance.[100]

Study (Year)	Group (N)	Surgical Wound Complications (N)	Overall Surgical Complications (N)	Surgical Complications (N)
Hirashima et al. (2012) **USA**	**Intervention** (N = 104)	3	21	Surgical Site Infection (n=3)
				Cardiac (n=16)
				Pulmonary (n=2)
				Stroke (n=NR)
				Graft Complication (n=0)
	Control (N = 189)	15	38	Surgical Site Infection (n=15)
				Cardiac (n=19)
				Pulmonary (n=2)
				Stroke (n=NR)
				Graft Complication (n=2)
Steely et al. (2017) **USA**	**Intervention** (N = 53)	15	24	Surgical Site Infection (n=15)
				Cardiac (n=7)
				Pulmonary (n=1)
				Stroke (n=1)
				Graft Complication (n=NR)
	N/A	-	-	-

N/A = Not Applicable; NR = Not Reported

Table 1. Summary of Primary and Secondary Outcomes

In terms of glucose intervention safety and efficacy, Hirashima et al. reported a hypoglycemic (glucose < 60 mg/dl) event rate of 19% of patients receiving insulin infusion without severe sequelae. Hyperglycemic events and effectiveness of glucose control in the intervention group was not reported on.[100] Steely et al. reported hypoglycemic events in 42% of patients (37% severe as defined by glucose < 70 mg/dl and 7% defined as severe by glucose < 50 mg/dl). Hyperglycemia with any glucose >250 ml/dl occurred in 44% of patients.[101]

With respect to secondary outcomes, there were a total of 45 postoperative complications (encompassing infectious, cardiac, and pulmonary etiologies).[100,101] However Hirashima et al., the one study comparing the intervention to a control group, did not report significant differences in post-operative complications between the two groups.[100]

Mean length of stay was reported in both studies with Hirashima et al. (n=1, 50%) demonstrating a significant reduction in patients with optimal glycemic control following an insulin infusion protocol (4.2 days vs. 7.3 days, p=0.02 as reported by the study).[100] No p-value was reported in Steely et al.'s study (5.9 days vs. 6.5 days, p= n.s.).[100]

Only Steely et al. (n=1, 50%)[101] reported on mortality in the intervention group (n=1/53, 1.9%) however neither study reported on long-term morbidity rates or re-intervention rates.

Discussion

Hyperglycemia commonly occurs in the surgical population as a result of stress-induced metabolic changes deregulating normal glucose homeostasis.[74,102] The induction of stress-hormones and pro-inflammatory cytokines results in a hyperglycemic state by inducing target tissue insulin resistance, breakdown in hepatic glycogen stores and hepatic neo-production of glucose.[102,103] Hyperglycemia has been shown to cause an increased morbidity and mortality

burden and to increase the risk of surgical site infections by up to 3-fold.[53,58-61] Conversely, perioperative insulin therapy to control glucose within a normal range has been shown to reduce perioperative complications, morbidity outcomes, and hospital resource utilization in the cardiac surgery population.[104-107] Given the high cost of managing surgical site infections following lower extremity vascular surgery, estimated to be in excess of $10,497 per patient in the in-patient setting alone,[48] the cost of perioperative glucose monitoring and control could be achieved for approximately $200 per patient as per our group's calculations.

At the cellular and molecular levels, hyperglycemic states alter the transport of ions within the smooth muscle endothelial cells of blood vessels, thus affecting myogenic function, vessel contractility and reactivity. Immune function is also compromised, with increases in circulating glucose leading to reduced cellular immunity and suppression of cytokine production in response to a threat.[55] Conversely, insulin, in addition to its metabolic role in reducing circulating glucose levels has known anti-inflammatory effects and is a positive inotrope.[108,109] Therefore, while the molecular changes associated with hyperglycemia account for poor patient outcomes, it is possible that the positive impact of perioperative insulin therapy may be accounted for by both the non-metabolic actions of insulin in addition to the glycemic control it affords.

While intensive insulin therapy has been regularly utilized in cardiac surgery, there is a paucity of data describing similar interventions in the vascular population. The current literature in vascular surgery largely consists of retrospective cohort data, but demonstrates a clear association between pre-, peri- and post-operative hyperglycemia to surgical wound infection rates. For example, elevated hemoglobin A1c (HbA1c), a marker that one of the included studies

reports on,[101] has consistently been shown to be predictive of major adverse limb events and hospital readmission in lower extremity revascularization.[110-113]

Although the studies presented here do not clearly demonstrate a decline in post-operative surgical site infections with strict glucose control, it should be noted that a large percentage of patients in the studies were not actually in the target range. The high incidence of hypo- or hyperglycemic events demonstrates a lack of efficiency and concerns for safety regarding the use of reactionary subcutaneous and intravenous insulin protocols. Further high-quality studies using effective and safe glucose control protocols, such as the glucose clamp test are required in order to properly characterize the impact of perioperative glucose control on infection rates, while maintaining a high standard of patient safety.

Limitations

This review has several limitations. Firstly, only two papers met the eligibility criteria, precluding a meaningful quantitative analysis. The lack of eligible studies meant that it was not feasible to generate a point effect estimate regarding the impact of a glucose control protocol on the primary outcome of surgical wound complications. Another additional limitation involves the biases of the included studies as they were evaluated to be of either moderate or serious risk of bias. Their degree of bias will ultimately impact the level of evidence assigned to their conclusions. Furthermore, as previously stated, only about half of the patients in the included studies remained in the targeted glucose range, preventing any meaningful interpretation of the effect of glycemic control on perioperative surgical site infection rates.

Conclusion

Despite evidence demonstrating a strong relationship between perioperative hyperglycemia and surgical site infections in the surgical literature, the impact perioperative glycemic control remains poorly studied within vascular surgery. Given the high rate of post-surgical infection following lower extremity vascular procedures, these patients could potentially benefit enormously from insulin-mediated glycemic control. However, existing studies in vascular surgery are underpowered and do not achieve reliable or safe glucose control. As the current literature on this topic is largely characterized by observational data, prospective, interventional data on perioperative glucose control is required to determine the effect that this could have on surgical site infection rates following infrainguinal vascular reconstruction.

Supplemental Tables

Supplemental Table 1. Search Strategy

#1) CINAHL November 15th - 755
Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus with Full Text
1946-2021

#	Query	Results
S37	S35 AND S36	755
S36	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S28	57,519
S35	S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34	94,883
S34	"postoperative blood glucose"	39
S33	"post-operative blood glucose"	6
S32	"pre-operative blood glucose"	1
S31	"preoperative blood glucose"	15
S30	"perioperative blood glucose"	35
S29	"peri-operative blood glucose"	4
S28	"infrainguinal"	253
S27	"glucose control protocol"	25
S26	"postoperative glucose"	48
S25	"post-operative glucose"	2
S24	"preoperative glucose"	19
S23	"pre-operative glucose"	5
S22	"peri-operative glucose"	2
S21	"perioperative glucose"	58
S20	"glycaemic control"	8,492
S19	"glycemic control"	21,449
S18	"glucose control"	3,807
S17	"insulin"	79,135
S16	"insulin infusion"	4,087
S15	"peripheral vascular disease"	6,931
S14	"peripheral artery disease"	6,194
S13	"peripheral arterial disease"	6,605
S12	(MH "Amputation+") OR "amputation"	14,633
S11	(MH "Limb Salvage") OR "limb salvage"	2,443
S10	"infra-inguinal"	45

S9	"chronic limb threatening ischaemia"	8
S8	"chronic limb threatening ischemia"	91
S7	"critical limb ischaemia"	113
S6	"critical limb ischemia"	933
S5	"Limb ischaemia"	267
S4	"Limb ischemia"	1,708
S3	"lower extremity bypass"	49
S2	"lower extremity revascularization"	109
S1	(MH "Vascular Surgery+") OR "vascular surgery"	34,293

#2) Clinical trials gov- November 15th, 2021: 166

(no limit filters)

(vascular surgery OR lower extremity revascularization OR lower extremity bypass OR limb ischemia OR amputation) AND (insulin infusion OR insulin OR glucose control OR glycemic control OR operative glucose)

#3) OVID MEDLINE – Search done on November 15th : 3063

(search done on november 15th but database most updated until november 12th)

Ovid MEDLINE(R) ALL <1946 to November 12, 2021>

1 exp Vascular Surgical Procedures/ or vascular surg*.mp. 280864
2 lower extremity revascularization.mp. 549
3 lower extremity bypass.mp. 434
4 (limb ischemia or limb ischaemia).ti,ab. 9952
5 (critical limb ischemia or critical limb ischaemia).ti,ab. 4343
6 (chronic limb threatening ischemia or chronic limb threatening ischaemia).ti,ab. 455
7 (infra-inguinal or infrainguinal).mp. 2376
8 limb salvage.mp. or exp Limb Salvage/ 9637
9 amputation.mp. or exp Amputation/ 50266
10 (peripheral arterial disease or peripheral artery disease or peripheral vascular disease).ti,ab. 23762
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 348710
12 (insulin or insulin infusion).mp. 438504
13 (glycemic control or glycaemic control).mp. 36901
14 (perioperative glucose or perioperative blood glucose).mp. 255
15 (peri-operative glucose or peri-operative blood glucose).mp. 21
16 (preoperative glucose or pre-operative blood glucose).mp. 99
17 (pre-operative glucose or pre-operative blood glucose).mp. 19
18 (postoperative glucose or postoperative blood glucose).mp. 262
19 (post-operative glucose or post-operative blood glucose).mp. 30
20 glucose control protocol.mp. 32
21 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 457442
22 11 and 21 3063

#4) COCHRANE November 15 (1908 – 15 November 2021) - 1782
ID Search Hits
#1 (vascular surg*) 16643
#2 lower extremity revascularization 297
#3 lower extremity bypass 254
#4 (limb ischemia OR limb ischaemia) 2512
#5 (critical limb ischemia OR critical limb ischaemia) 1023
#6 (chronic limb threatening ischemia OR chronic limb threatening ischaemia) 97
#7 infra-inguinal OR infrainguinal 291
#8 limb salvage 500
#9 amputation 3207
#10 (peripheral arterial disease OR peripheral artery disease OR peripheral vascular disease):ti,ab 6084
#11 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 #10 18795
#12 (insulin infusion OR insulin) 65981
#13 glucose control 32865
#14 (glycemic control or glycaemic control) 17738
#15 perioperative glucose OR peri-operative glucose OR perioperative blood glucose OR peri-operative blood glucose 3127
#16 preoperative glucose OR pre-operative glucose OR preoperative blood glucose OR pre-operative blood glucose 6595
#17 postoperative glucose OR post-operative glucose OR postoperative blood glucose OR post-operative blood glucose 24104
#18 glucose control protocol 3372
#19 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 108094
#20 #11 AND #19 1783

#5) Web of Science
Web of Science november 15, 2021 – 3128 - web of science Core Collection 1900 to present (all editions)
History
36 (#35) AND #20 3,128
35 ((((((((((((#34) OR #33) OR #32) OR #31) OR #30) OR #29) OR #28) OR #27) OR #26) OR #25) OR #24) OR #23) OR #22) OR #21 517,156
34AB=(glucose control protocol) 3,304
33 TI=(glucose control protocol) 127
32AB=(postoperative glucose OR post-operative glucose) 3,406
31 TI=(postoperative glucose OR post-operative glucose) 283
30 AB=(preoperative glucose OR pre-operative glucose) 2,240
29 TI=(preoperative glucose OR pre-operative glucose)164
28 AB=(perioperative glucose OR peri-operative glucose) 1,224
27 TI=(perioperative glucose OR peri-operative glucose) 232
26 AB=(glycemic control OR glycaemic control) 36,774

25 TI=(glycemic control OR glycaemic control) 14,085
24 AB=(glucose control) 132,567
23 TI=(glucose control) 8,183
22 AB=(insulin infusion OR insulin) 290,290
21 TI=(insulin infusion OR insulin) 216,786
20 ((((((((((((((((#1) OR #2) OR #3) OR #4) OR #5) OR #6) OR #7) OR #8) OR #9) OR #10) OR #11) OR #12) OR #13) OR #14) OR #15) OR #16) OR #17) OR #18) OR #19 155,022
19 AB=(peripheral arterial disease OR peripheral artery disease OR peripheral vascular disease) 32,737
18 TI=(peripheral arterial disease OR peripheral artery disease OR peripheral vascular disease) 13,419
17 AB=(amputation) 28,608
16 TI=(amputation) 10,868
15 AB=(limb salvage) 6,213
14 TI=(limb salvage) 1,790
13 AB=(infra-inguinal OR infrainguinal) 1,814
12 TI=(infra-inguinal OR infrainguinal) 1,264
11 AB=(chronic limb threatening ischemia OR chronic limb threatening ischaemia) 467
10 TI=(chronic limb threatening ischemia OR chronic limb threatening ischaemia) 299
9 AB=(critical limb ischemia OR critical limb ischaemia) 4,629
8 TI=(critical limb ischemia OR critical limb ischaemia)3,007
7 AB=(limb ischemia OR limb ischaemia) 12,358
6 TI=(limb ischemia OR limb ischaemia) 6,304
5 AB=(lower extremity bypass) 1,635
4 TI=(lower extremity bypass) 467
3 AB=(lower extremity revascularization)1,306
2 TI=(lower extremity revascularization)417
1 TI=(vascular surg*) OR AB=(vascular surg*) 76,059

#6) Embase+embase classic 1947 – nov 15 2021 - **2896**
Embase Classic+Embase <1947 to 2021 Week 45>

1	vascular surg*.ti,ab. 29017
2	lower extremity revascularization.mp. 784
3	lower extremity bypass.mp. 663
4	(limb ischemia or limb ischaemia).ti,ab. 15550
5	(critical limb ischemia or critical limb ischaemia).ti,ab. 7094
6	(chronic limb threatening ischemia or chronic limb threatening ischaemia).ti,ab. 612
7	(infra-inguinal or infrainguinal).mp. 3264
8	limb salvage.ti,ab. or exp Limb Salvage/ 12498
9	amputation.ti,ab. or exp Amputation/ 78961
10	(peripheral arterial disease or peripheral artery disease or peripheral vascular disease).ti,ab. 38601
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 152867
12	(insulin or insulin infusion).ti,ab. 526855

13	(glycemic control or glycaemic control).ti,ab.	58582
14	(perioperative glucose or perioperative blood glucose).mp.	380
15	(peri-operative glucose or peri-operative blood glucose).mp.	38
16	(preoperative glucose or pre-operative blood glucose).mp.	165
17	(pre-operative glucose or pre-operative blood glucose).mp.	39
18	(postoperative glucose or postoperative blood glucose).mp.	381
19	(post-operative glucose or post-operative blood glucose).mp.	75
20	glucose control protocol.mp.	54
21	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	557728
22	11 and 21	2896

Supplemental Table 2: Excluded articles and rationale for exclusion

Article	Title	Author	Year	Reason for Exclusion
1	The association of postoperative glycemic control and lower extremity procedure outcomes	Vogel et al.	2017	Not appropriate intervention/ no intervention
2	Use of a postoperative insulin protocol decreases wound infection in diabetic patients undergoing lower extremity bypass	Hirashima et al.	2011	Abstract
3	Continuous perioperative insulin infusion decreases major cardiovascular events in patients undergoing vascular surgery: a prospective, randomized trial	Subramaniam et al.	2009	Not appropriate population (pooled outcomes amongst other surgery types)
4	Evaluation of the Bundle "Zero Surgical Site Infection'' to Prevent Surgical Site Infection in Vascular Surgery	Fernandez-Prada et al.	2017	Not appropriate intervention/ no intervention
5	Effect of intensive glycemic control on risk of lower extremity amputation	Goldman et al.	2019	Not appropriate intervention/ no intervention

Supplemental Table 3. Demographic Information

Study (Year)	Group (N)	Age (years) (M±SD)	Male (N, %)	Female (N, %)	BMI (M±SD)	Ever Smoker (N, %)	Race* (N, %)
Hirashima et al. (2012) **USA**	**Intervention** (N = 104)	64.3 ± 9.7	83 (81%)	21 (20%)	27.3 ± 4.5	97 (93%)	NR
	Control (N = 189)	65.2 ± 11.6	140 (74%)	49 (26%)	29.2 ± 6.1	168 (89%)	NR
Steely et al. (2017) **USA**	**Intervention** (N = 53)	NR	43 (81%)	10 (19%)	NR	50 (94%)	49 (92%) / 4 (8%)
	N/A	-	-	-	-	-	-

*White / Non-White
BMI = Body Mass Index; M±SD = Mean ± Standard Deviation; N/A = Not Applicable; NR = Not Reported.

Supplemental Table 4. Medical Comorbidities at Baseline

Study (Year)	Group (N)	Diabetes (N, %)	Dyslipidemia (N, %)	CAD (N, %)	HTN (N, %)	CHF (N, %)	COPD/PULM (N, %)	ESRD/Renal (N, %)
Hirashima et al. (2012) **USA**	**Intervention** (N = 104)	44 (42%)	82 (81%)	NR	86 (83%)	2 (2%)	16 (16%)	4 (4%)
	Control (N = 189)	90 (48%)	122 (65%)	NR	160 (85%)	9 (5%)	26 (14%)	6 (3%)
Steely et al. (2017) **USA**	**Intervention** (N = 53)	27 (51%)	43 (81%)	19 (37%)	43 (81%)	4 (8%)	8 (15%)	5 (10%)
	N/A	-	-	-	-	-	-	-

CAD = Coronary Artery Disease; CHF = Congestive Heart Failure; COPD/PULM = Chronic Obstructive Pulmonary Disease/ Pulmonary Disease; ESRD/Renal = End-stage Renal Disease/Renal Disease; HTN = Hypertension; N/A = Not Applicable.

Supplemental Table 5. Indications for Revascularization

Study (Year)	Group (N)	Asymptomatic (N, %)	Claudication (N, %)	CLTI (N, %)	Venous Graft (N, %)	Prosthetic Graft (N, %)
Hirashima et al. (2012) **USA**	**Intervention** (N = 104)	11 (11%)	34 (33%)	56 (54%)	78 (75%)	26 (25%)
	Control (N = 189)	20 (11%)	40 (21%)	118 (62%)	158 (84%)	31 (16%)
Steely et al. (2017) **USA**	**Intervention** (N = 53)	NR	18 (34%)	33 (62%)	42 (79%)*	10 (19%)
	N/A	-	-	-	-	-

*Single and composite graft

CLTI = Chronic Limb-Threatening Ischemia; N/A = Not Applicable; NR = Not Reported.

7 Discussion

The previous manuscripts highlight a gap in patient care with significant impact on patient outcomes. Unfortunately, the most appropriate solution to perioperative hyperglycemia remains unclear. Current protocols for subcutaneous insulin sliding scales are not uniformly prescribed and are designed to avoid hypoglycemia, thus frequently failing to prevent hyperglycemia.[86] We demonstrated that only a small fraction of our cohort underwent intra-operative glycemic surveillance, however this does not necessarily indicate that intra-operative surveillance will necessarily improve outcomes. One study protocolizing intra-operative surveillance did indeed find reduced infection rates in individuals who were monitored regularly intra-operatively, however more data is needed to confirm these findings.[85] The cohort that underwent intra-operative surveillance in our study represented 3.9% of the total participants and thus was too small to perform sub-analysis on. Understanding the true impact of intra-operative glycemic surveillance would therefore require data acquired from a well-designed prospective study or a larger retrospective cohort of patients who underwent intra-operative glycemic surveillance. Other efforts to control blood glucose such as the use of intensive glycemic control, pre-operative carbohydrate loading, avoiding extensive fasting and the use of continuous glucose monitors have been found to be beneficial but have not been validated in a vascular patient population.[55,63,88] Overall, optimizing perioperative glycemia will likely require multimodal management, however the exact recipe for success remains to be determined.

While the retrospective review characterized patients with glycemic values above 10 mmol/L as hyperglycemic, it remains worth noting that it is unclear what the safest and most beneficial target for a glycemic control measure should be. Currently, the McGill University Health Centre insulin sliding scale targets a blood glucose range of 4 to 10 mmol/L. However, normal individuals typically maintain a fasting blood glucose of 3.3 to 5.5

mmol/L.[114] Even societal guidelines differ significantly in terms of glycemic target recommendations. The American Diabetes Association suggests a general target blood glucose of 5.6-10 mmol/L but also suggests that stricter targets may be more appropriate in select patients.[82] Several studies have found that even a small rise in glycemia above normal can be harmful. McAlister et al found that even a 1 mmol/L increase in blood glucose level above 6 mmol/L led to a 17% increase mortality post cardiac surgery, indicating that a much stricter target might be necessary.[64,93] Conversely, studies of intensive insulin therapy targeting 8 mmol/L have been found to be beneficial.[65] The ideal glycemic target thus remains unclear.

Rather than targeting a maximum blood glucose, variability in glycemic measurements during admission might also be a viable target to improve patient outcomes. Glucose level variability has also been found to contribute to an increased risk of complications, regardless of whether hyperglycemia occurred or not.[115,116] Interestingly, one study demonstrated in a cohort of 7049 patients in a mixed medical and surgical intensive care setting demonstrated that variability had a larger impact on morbidity and mortality than mean blood glucose.[115]

It thus seems that lower glycemic targets and tighter acceptable glycemic ranges would be ideal based on this information. Unfortunately, effectively targeting these values with insulin protocols increases the rate of hypoglycemia, which has been significantly associated with increased mortality.[117] The brain relies solely on glucose to fuel its functions and in the presence of severe hypoglycemia neuronal necrosis occurs which can lead to seizures, coma or mortality.[118] Avoiding this severe complication while effectively targeting hyperglycemia therefore remains a significant challenge. Further studies are needed to address the challenges of what glycemic targets and ranges are appropriate and how insulin

protocols can be designed to maintain patients within these ranges while avoiding dangerous hypoglycemic events.

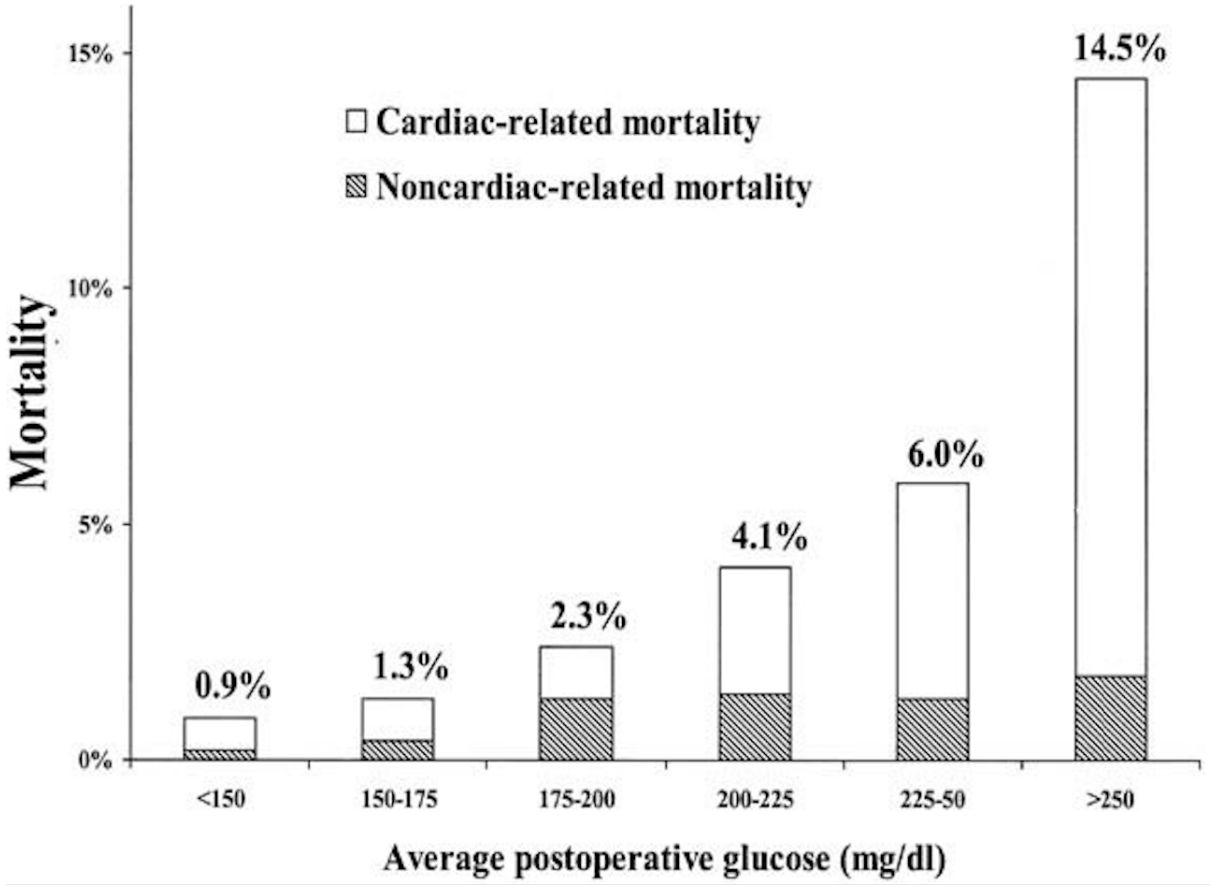


Figure 2. Mortality post coronary artery bypass grafting separated by average post-operative glucose in quantiles. Every 1 mmol/L increase above 6.1 mmol/L was associated with a 17% increase in perioperative mortality. (Excerpted from Furnary et al, Cardiopulmonary Support and Physiology, 2003 – Permission for use obtained from publisher).

One potential tool for using insulin to accurately and effectively maintaining normoglycemia while avoiding hypoglycemia intra-operatively or in the acute care setting might be the normoglycemic-hyperinsulinemic clamp protocol. This protocol infuses a weight-based constant rate of intravenous insulin while simultaneously infusing a solution of dextrose at a variable rate.[119] The rate of dextrose infusion can be adjusted according to glucose measurements, leading to a swift change in glucose value. Conversely, the medium-

acting insulin agents used in most sliding scale protocols take approximately 20 minutes to take effect. The result is a real-time ability to accurately target a specific glucose value. Most importantly this protocol is also safe, given the continuous dextrose infusion hypoglycemia is easily avoided, with one study demonstrating hypoglycemic events occurring in only 0.1% of patients.[120,121] Furthermore, because in a normoglycemic state the glucose infusion rate equals the glucose uptake by all the tissues in the body, a patient's degree of whole-body insulin sensitivity can be calculated.[119] This is achieved by calculating the M-value or mean glucose infusion rate.[119] This could theoretically be used to identify patient at risk of post-operative hyperglycemia and allow them to be more closely monitored and aggressively treated for this. This would also allow identification of patients who are not diabetic but experience "stress hyperglycemia" without a pre-existing elevated hemoglobin A1c or a diagnosis of diabetes. Lastly, one further benefit of this intervention may have nothing to do with glycemic control. Insulin has been shown to provide anti-inflammatory, positive inotropic and cardioprotective benefits independent of glycemic control.[108,109]

It also bears remembering that intra- and post-operative glycemic control remains only a small target of improving glycemic control of the general population. Interventions and surveillance in the perioperative period geared towards glycemic control will reduce the risk of acute hyperglycemia, which is an independent risk factor for morbidity and mortality, but overall long-term glycemic control remains important. Following a femoral endarterectomy, for example, patients are frequently discharged on post-operative day one, whereas even post-bypass most patients will stay for a maximum of 5 days post-operatively. This encompasses only a small proportion of time in over which glycemic control can be optimized. Hemoglobin A1c is a glycosylated hemoglobin molecule which reflects the average blood glucose over the past 2-3 months. An HbA1c of 5.6% or lower is normal, however values above 6.5% are diagnostic for diabetes mellitus.[83] Unfortunately our review

demonstrated that at McGill at least, many patients underwent surgery without a recent HbA1c, even though most patients are seen by a pre-operative medicine consultant prior to their procedure for pre-operative optimization and the pre-existing body of literature linking elevated HbA1c to poor perioperative outcomes. Sato et al demonstrated that a HbA1c above 6.5% correlated with insulin resistance perioperatively and increased the risk of major complications by 17% and the risk of minor infections by 29% following cardiac surgery.[122] Improvements in long-term glycemic management by primary care physicians and endocrinologists are therefore important to improving poor patient outcomes.

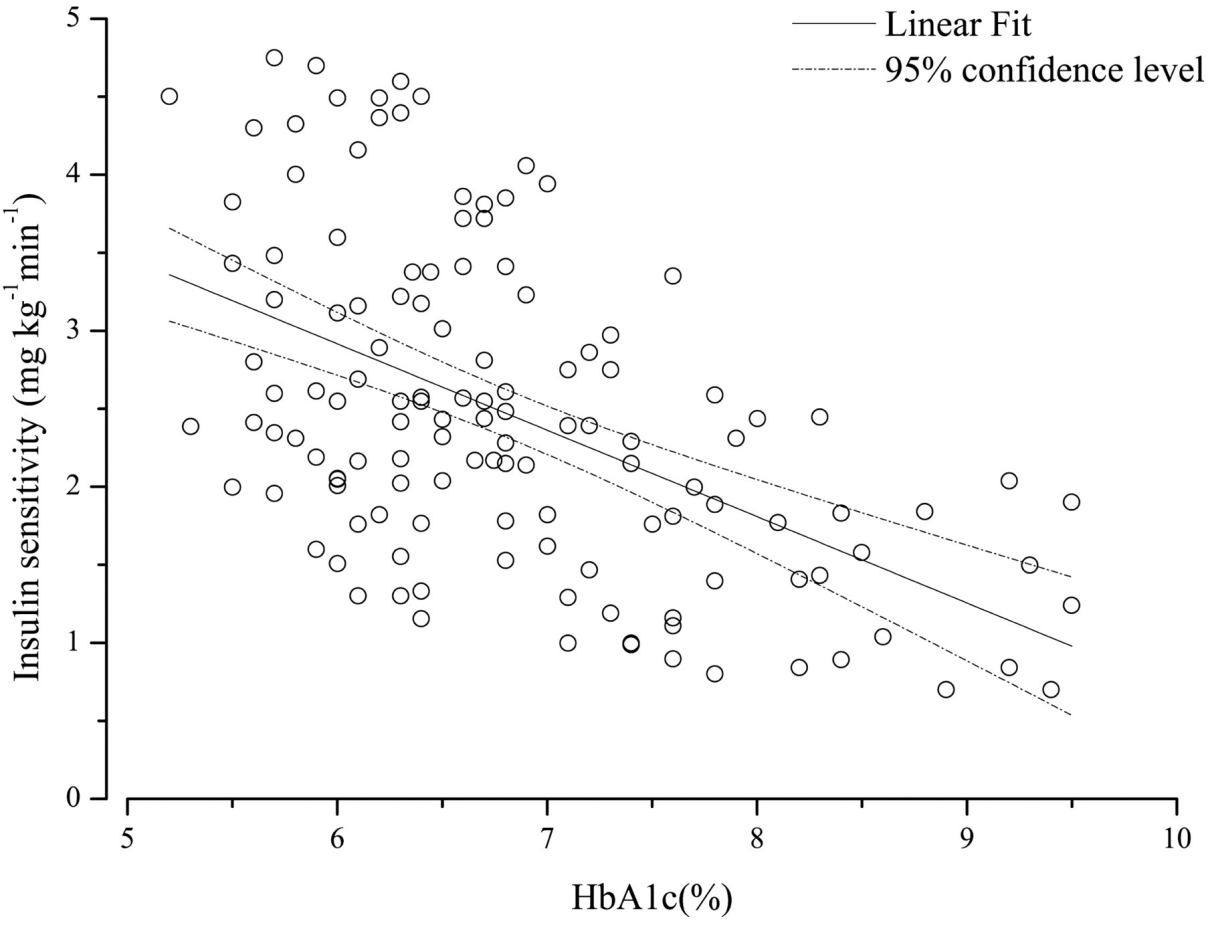


Figure 3 Association between preoperative HbA1c levels (%) and insulin sensitivity during cardiac surgery. Excerpted from Sato et al, Journal of Clinical Endocrinology and Metabolism, 2010 – Permission for use obtained from publisher.

Future prospective studies evaluating the use of glycemic control measures in vascular surgery are necessary to fully evaluate the impact that tighter glycemic control could have on perioperative outcomes. While we recognize that optimal perioperative glycemic control will likely be multimodal, individual therapies need to be assessed independently in the vascular surgery context to be accumulate the data needed to make treatment decisions. As a follow up to the work presented in this thesis we have begun a trial examining the potential impact of intensive insulin therapy on patients undergoing vascular surgery. Our centre is currently enrolling patients for a prospective study examining this topic. Using a permissive range of 4 to 8 mmol/L, enrolling non-critically ill patients and using a combination of an intra-operative euglycemic clamp protocol intra-operatively and a modified subcutaneous insulin sliding scale post-operatively, we hope to be able to avoid the elevated risk of hypoglycemic events noted in previous studies while also accurately and successfully maintaining euglycemia. In this way we hope to be able to contribute to the future of perioperative glycemic control. The potential benefit for improving glycemic control is too large to ignore. Decreasing healthcare costs both during hospital admission and post-discharge, decreasing healthcare personnel and resource requirements, improving patient ability to maintain independence and quality of life in their senior years remains a paramount motivator for continuing to research this topic. Further data generation is needed to establish glycemic targets and protocols which can be standardized for safe and efficacious use across this vulnerable population and incorporated into widely-accepted and used guidelines.

8 Final Conclusion and Summary

Patients with peripheral arterial disease requiring lower extremity revascularization or amputation are at high risk of perioperative complications due to their medical complexity. High rates of pre-existing diabetes or underlying insulin resistance as well as the physiologic stress of revascularization means that perioperative hyperglycemia occurs frequently in this

population. Perioperative glycemic intervention represents a potential target for reducing the risk of surgery but has not been sufficiently evaluated with prospective studies in this patient population.

We sought to identify the need for improved perioperative glycemic surveillance and control at our institution by describing current practices in intra- and post-operative glycemic surveillance, treatment patterns and efficacy of these interventions. In addition to demonstrating a lack of consistent surveillance, we demonstrated that a large proportion of patients were hyperglycemic during their admission despite measures taken to improve their control. Furthermore, these patients were more likely to experience 30-day mortality and other complications. We therefore recognize the need for more aggressive and standardized surveillance and treatment regimens to maintain patients at safe glycemic levels.

Our next objective was to evaluate the pre-existing literature on one intervention that has demonstrated promising results in the cardiac surgery literature. We performed a systematic review to assess the data available on the use of intensive insulin therapy in vascular surgery. Overall, our results demonstrated a paucity of data with only two studies with varying protocols and success in maintaining normoglycemia. This variability and lack of adherence to the intervention makes it impossible to draw conclusions from these studies. We therefore recognize the need for further prospective studies with well-designed protocols to properly assess the role of intensive insulin therapy in the vascular surgery milieu.

Glycemic control in the perioperative period is a complex topic. While initially overlooked and even thought to be beneficial, it is now well-established that hyperglycemia is a significant contributor to poor outcomes. Many factors contribute to hyperglycemia and therefore the solution to obtaining safe and effective glycemic control in most patients will likely be as nuanced as the causes. The work done in this thesis will hopefully serve as a

foundation for future work on interventions which can help achieve glycemic control, reduce rates of morbidity and mortality, and ultimately improve the safety and quality of vascular surgical care.

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