UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

University of Pretoria
Faculty of Health Sciences
Department of Nursing

MANAGEMENT STRATEGIES OF DYSGLYCAEMIA IN CRITICALLY ILL ADULT PATIENTS: A SCOPING REVIEW

A dissertation in fulfilment of the requirements for the degree Master of Nursing Sciences
(M.Nurs)

Lüschke Geldenhuys

Supervisor: Prof C. Filmalter

Co-supervisor: Prof T. Heyns

Date of submission: November 2023

DECLARATION

I, Lüschke Geldenhuys, declare that this dissertation, titled ***'Management strategies of dysglycaemia in critically ill adult patients: a scoping review'***, is my original work. It has not been submitted to any other institution before for any degree or examination. All the sources used and quoted are acknowledged by means of complete references in the text and bibliography.

……  …… ……8.12.23……..

Researcher signature Date

……  …… ……8.12.23……...

Witness Date

DEDICATION

To my love, Hannes – you always believed I could, and I did.

Lvj

xxx

ACKNOWLEDGEMENTS

Thank you to my Father, for gifting me with an equipped mind and heart to see this journey through.

Thank you to my supervisor Prof. Celia Filmalter. You have guided and supported me throughout this whole process. Thank you for the endless office visits (with coffee of course), the emails, and chats when I felt I could not carry on anymore. And of course, all the late night and early calls of encouragement and pick-me-ups [Mama bear 😉]. You have made this easier for me and I appreciate it more than I can say.

To my parents, brother and sisters, friends, and family, for understanding all the hours of work that was put into this study. All the times I called off visits and needed time alone. Thank you for your understanding and for your support throughout this journey.

To the rest of the team who supported and assisted me throughout the preparation of this thesis, Mrs. Estelle Grobler, Mr. Sagren Naidoo, Mrs. Christel Jordaan and Dr. Carel Viljoen, Mr. Luan Nel; your efforts did not go unnoticed.

And last, but not least, my love, Hannes. You have been there every step of the way, wiping tears, bringing coffee, and staying up late to sit and work with me. You showed me ways when I thought there was no way anymore. You have encouraged me every day and you were always there to help me. I look up to you and I admire your determination. I love you so much.

SYNOPSIS

Title: Management strategies of dysglycaemia in critically ill adult patients: a scoping review.

Background: Dysglycaemia comprises of hypoglycaemia, hyperglycaemia and glycaemic variability. It is a biomarker of disease severity and my lead to increased mortality in critically ill patients. Dysglycaemia is common in critically ill patients and also presents in non-diabetic patients. However, blood glucose/dysglycaemia management strategies for critically patients remain ad hoc, which increases the risks for complications associated with dysglycaemia.

Objective: The objective of the study was to explore, identify and map the evidence available on management strategies of dysglycaemia in critically ill adult patients in the critical care unit, and to identify evidence gaps relating to the management of dysglycaemia in critically ill adult patients.

Design: A Scoping review was done according to the Joanna Briggs Institute (JBI) methodology.

Data source and search strategy: Medline and CINAHL databases were searched to identify articles that examine glucose control in the critical care unit (CCU). Articles that were published from 2001 until 2023 were evaluated and the search was limited to articles published in English. We used the following search terms: *Glucose monitoring OR glucose control OR glycaemic control OR dysglycaemia NOT Diabetes mellitus OR Diabetes OR Diabetic AND Critically ill OR intensive care patients OR critical care patients.* Only original articles were included while case reports as well as editorial letters, opinion papers, and surveys were excluded. The search strategy was compiled by the author and an experienced information specialist executed the search.

Eligibility criteria and study selection: *Population* - (i) patients 18 years or older, (ii) female and male patients, (iii) patients of any race and ethnicity, (iv) patients admitted to the critical care unit following a medical or surgical diagnosis, (v) studies from 2001 up to 2023. *Concept* – Sampling method of blood glucose, frequency monitored, target range of blood glucose guiding treatment (hypo or hyper), method of Insulin or Dextrose administration, evaluation. *Context* – Critical care units and high care units. All publications were screened by the researcher and a supervisor. Results were discussed, and the screening and data extraction process was amended as

necessary, before making final decisions. Titles, abstracts, and full texts of all the publications were screened by the researcher and supervisor independently to ascertain inclusions. Disagreements were settled without the need for a 3rd party involvement.

Once the results were available, it was exported into EndNote and Rayyan, an online systematic review software. Duplicates were removed by the researcher, and articles were reviewed for inclusion and exclusion. Additional relevant material was not deemed necessary, so no authors were contacted during this period. Lastly, reference lists were searched and screened for potential sources.

Data extraction: A data charting form was created in Excel and data extraction variables were drawn up as columns. This was done to ensure important details were not omitted and to ensure that the data captured were in line with the study's objectives and inclusion criteria. The data charting form was continuously updated. With the aid of a data extraction tool created for this study, the data from the eligible studies were then charted. The form was used to capture all the relevant data and specific key characteristics regarding included variables of blood glucose control. Only one reviewer charted the results independently and these were reviewed by another reviewer. Disagreements were solved through discussion.

Results: The primary search strategy identified 2261 potentially relevant papers (see *Figure 2*). Duplicates were removed at this stage (in Rayyan), and a total of 1908 articles remained. Articles which had restricted access to full text was 160. A total of 1748 records remained at this stage. The titles and abstracts, as well as full-text articles were screened, of which 1732 were excluded. The selection at this stage included 16 studies. Two (2) additional studies were identified through a manual search of the reference lists of these studies. Uncertainty existed over the optimum treatment goal for glycaemia in the critically ill population. The largest prospective multicenter trial, which revealed an increase in mortality in patients receiving intense insulin therapy, could not duplicate the findings of randomized controlled trials from the early 2000s that showed a benefit of very tight glucose control. The present research largely focused on the clinical benefit and hypoglycaemia risk of intensive insulin therapy; however, there was no consensus on the ideal blood glucose control range, the patients who should receive it, when to initiate treatment, and how to minimize the risk.

Conclusion: There's more to blood glucose measurement than meets the eye. It is much more comprehensive and is not as simple as sampling blood for testing, and a lot of factors need to be taken into consideration. There are many diverse and different views regarding target range of blood glucose, frequency of testing, and sampling of blood. Conclusions cannot simply be drawn from the articles as there were too many diverse views and results.

KEY WORDS: critically ill, critical care unit, dysglycaemia, glucose control, management strategies

TABLE OF CONTENT

LIST OF TABLES

LIST OF FIGURES

LIST OF ANNEXURES

Chapter 1: Introduction

The aim of this chapter is to give an overview and background on blood glucose to provide insight into the importance of blood glucose and the role it plays in different bodily functions. An introduction to dysglycaemia and its components and risk factors are given. The research problem, aims and objectives are briefly outlined, followed by the design of the study and significance thereof. Key concepts in the thesis are defined, followed by an outline of the chapters to follow in the thesis to conclude this chapter.

1.1 Background

Blood glucose is essential to support life as it is needed to maintain normal metabolic processes. Blood glucose is therefore an important part of clinical monitoring, as it is a prognostic parameter for any disease (Kesavadev, Misra, Saboo, Aravind, Hussain, Czupryniak et al., 2021). Blood glucose monitoring is part of vital signs and are measured in hospital patients to assess the state of a patient's essential body functions. Metabolic and glucose equilibrium is seen as part of that essential function, and thus serum glucose level is regarded as the fifth vital sign (Fortmann, Spierling Bagsic, Talavera, Garcia, Sandoval, Hottinger et al., 2020). Critically ill patients are prone to dysglycaemia, which comprises the following domains: hypoglycaemia, hyperglycaemia, and glycaemic variability. It is a biomarker of disease severity and leads to increased mortality in critically ill patients (Aramendi, Burghi and Manzanares, 2017).

Patients admitted to the critical care unit (CCU) frequently present with dysglycaemia. Research has shown numerous negative effects of impaired glycaemic control in patients undergoing surgery and admitted to the CCU over the past few decades (Sreedharan, Martini, Das, Aftab, Khanna and Ruetzler, 2022). Blood glucose levels before or during CCU admission were positively correlated with death in critically ill patients (Lee, Drake, Roberts, Bersten, Stranks, Heilbronn et al., 2020). According to the findings of an epidemiological study conducted in the United States, 9.3% of non-diabetic patients had increased mean daily glucose levels on admission to the CCU (Wu, Liu, Zhang, Kang, Zuo, Xu et al., 2022).

In a multicentre prospective pivotal trial done at four United States academic centres, at least 51% of critically ill patients had at least one episode of dysglycaemia (Bochicchio, Nasraway, Moore, Furnary, Nohra, Bochicchio et al., 2021). Since most research on dysglycaemia in people living with HIV comes from high-income countries (HIC), it is unclear how much of the risk factors associated with dysglycaemia burden, morbidity, and mortality that have been identified can be applied to Sub-Saharan African populations (Njuguna, Kiplagat, Bloomfield, Pastakia, Vedanthan and Koethe, 2018). Levitt, Peer, Steyn, Lombard, Maartens, Lambert et al. (2016) observed a higher prevalence of dysglycaemia in South African people living with HIV who were not on antiretroviral therapy (22%), people living with HIV who were on first line antiretroviral therapy (26%), and people living with HIV who were on second line antiretroviral therapy (37%) (Njuguna et al., 2018). In West Africa, there are limited population data on dysglycaemia (Enang, Otu, Essien, Okpara, Fasanmade, Ohwovoriole et al., 2014)

.

The risks associated with chronic dysglycaemia, such as renal and long-term cardiovascular complications are well described and are connected to an increased risk for in-hospital complications (Balintescu, Palmgren, Lipcsey, Oldner, Larsson, Cronhjort et al., 2021). The domains of dysglycaemia are regarded as independent predictors of adverse outcomes in critically ill patients (Sanaie and Mahmoodpoor, 2017).

Dysglycaemia in critical illness is caused by endogenous glucose production and impaired counterregulatory response. This is exacerbated by contributing factors in the CCU leading to hypoglycaemia, hyperglycaemia, and glucose variability (Plummer, Hermanides and Deane, 2022). A variety of drugs used in the CCU such as glucocorticoids, catecholamine drugs, and others, together with the stress response, contribute to dysglycaemia in critically ill patients (Joshi and Mehta, 2022).

The first randomized controlled trial which was done in Leuven, found that intensive insulin therapy and tight glucose control had shown decreased mortality and morbidity in critically ill patients (Van den Berghe, Wouters, Weekers, Verwaest, Bruyninckx, Schetz et al., 2001). The findings were confirmed using medical-surgical patients in a

trial by Van den Berghe, Wilmer, Hermans, Meersseman, Wouters, Milants et al. (2006), and Krinsley (2004b).

However, the NICE-SUGAR trial (Normoglycaemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation), found that more 'tight glucose control' increased the risk for hypoglycaemia and that intensive insulin therapy increased mortality. Management of dysglycaemia then aimed for 'moderate' blood glucose ranges of 7.7-10mol/L (Krinsley and Preiser, 2019; Sreedharan et al., 2022).

Based on contrasting intensive insulin therapy to traditional glucose management over the past two decades, glycaemic goals for critically sick patients have changed over time (Sreedharan et al., 2022). The treatment of dysglycaemia appears to have evolved over the years, but to prevent death or morbidity, it is crucial that critically ill patients receive the best and safest care possible upon diagnosis. Few research has examined the literature on how to explore and map the different management strategies of dysglycaemia in the critically ill adult patient.

1.2 Research problem

Currently, little is known about dysglycaemia in low-income nations (Nakiriba, Mayega, Piloya, Nabukeera-Barungi and Idro, 2018). Optimal blood glucose control is necessary, therefore blood glucose measurements should be done accurately, frequently and promptly (See, 2021). There should be adherence to glycaemic protocols to avoid hypoglycaemia. It is suggested that to prevent hyperglycaemia or hypoglycaemia, intensive glucose management and monitoring should be implemented and glycaemic control protocols should be adhered to (See, 2021). In the researcher's clinical environment (adult CCU), there is no set protocol or best practice guideline for the management of dysglycaemia. Blood glucose levels are managed based on individual experiences and the knowledge of nurses working in the unit, resulting in a lack of a uniform approach to management strategies.. Thus, to create uniformity in terms of the management of dysglycaemia, a scoping review is needed to identify current best evidence-based practices in this regard.

1.3 Research question

How is dysglycaemia managed in the critically ill adult patient in the critical care unit?

1.4 Aim

The aim of the study was to explore different management strategies of dysglycaemia in the critically ill adult patient.

1.5 Objectives

The objectives of the study were:

- To explore, identify, and map the evidence available on management strategies of dysglycaemia in the critically ill adult patient in the critical care unit.
- To identify evidence gaps relating to the management of dysglycaemia in the critically ill adult patient.

1.6 Research design

A scoping review was done for this research. The methodological framework and recommendations of the Joanna Briggs Institute (JBI) were specifically used as it provided an overview of a broad topic serving the following purpose: to explore different management strategies of dysglycaemia in critically ill patients in a critical care unit. This review was completed in terms of the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines.

1.7 Significance / contribution

In line with the aim of the study, the findings of the scoping review might be used to enable and educate critical care nurses as well as the rest of the multidisciplinary team regarding the management of dysglycaemia in the critically ill adult patient. It may also stimulate further research for the generation of an evidence-based practice guideline in the management of dysglycaemia. Gaps for further research chould become evident in the review. Policy makers may be involved to start the process of protocol development.

1.8 Assumptions

The researcher assumed that the search strategy given by the information specialist was comprehensive enough to include the most relevant articles. A further assumption

that could be made was that information gathered from the evidence was correct and accurate.

1.9 Definition of key terms / concepts

Key term/ definition	Conceptual definition	Operational definition
Critical care unit (CCU)	"An intensive care (also known as critical care) unit is an organized system for the provision of care to critically ill patients that provides intensive and specialized medical and nursing care, and enhanced capacity for monitoring, and multiple modalities of physiologic organ support to sustain life during a period of life-threatening organ system insufficiency." (Marshall, Bosco, Adhikari, Connolly, Diaz, Dorman et al., 2017:270).	For the purpose of this study the CCU includes the intensive care unit (ICU) and high care unit (HCU). Hospital units known as high care units provide patient care at a level that falls between that of an intensive care unit and a general ward (Ohbe, Matsui and Yasunaga, 2021).
Blood glucose	Blood glucose is the most important carbohydrate fuel found in the body. Circulating blood glucose in the fed state, comes from a person's diet, whereas blood glucose is maintained by gluconeogenesis and glycogenolysis in the fasting state. Blood glucose is found in more complex carbohydrates broken down to monosaccharides through digestion (McMillan, 1990).	This definition will be adopted for the purpose of this study.
Dysglycaemia	According to (Balintescu et al., 2021), patients who are critically ill, present with hyperglycaemia, hypoglycaemia and/or distinct	For the purpose of this study dysglycaemia refers to critically ill

	fluctuations in blood glucose. These components are termed as dysglycaemia and commonly manifests in critically ill patients, as well as in the non-diabetic patients (Joshi et al., 2022).	patients managed in the CCU who present with hyperglycaemia, hypoglycaemia and/or distinct fluctuations in blood glucose.
Critically ill patient	Patients admitted to the CCU who required mechanical ventilation, inspired oxygen concentration via a face mask that was greater than or equal to 60%, or inotropic drugs are considered critically ill (Fowler, Lapinsky, Hallett, Detsky, Sibbald, Slutsky et al., 2003).	For the purpose of this study a critically ill patient is a person 18 years or older admitted to CCU with a medical or surgical condition which requires continuous monitoring.
Insulin	Insulin is a peptide hormone that is secreted by the pancreatic islets of Langerhans cells. It regulates carbohydrate, lipid, and protein metabolism, facilitates cellular glucose uptake, and promotes cell division and proliferation through its mitogenic effects (Wilcox, 2005). Insulin is a drug that increases protein synthesis, promotes peripheral glucose uptake, suppresses the production of glucose in the liver, prevents adipocyte lipolysis, and inhibits proteolysis (Weiner and Buhimschi, 2009).	For the purpose of this study, insulin will be defined as a medical drug, given by a healthcare provider to a patient.
Central venous blood	Blood drawn via a central venous catheter is referred to as central venous blood. Central venous catheters are often inserted cutaneously into the superior vena cava through the jugular vein in the neck or the	This definition will be adopted for the purpose of this study.

	subclavian vein in the upper chest (Higgins, 2011).	
Capillaries	Capillaries are blood vessels with thin walls that carry nutrients and metabolites from the vasculature into the interstitium where cells can absorb them (Godwin, Tariq and Crane, 2023).	This definition will be adopted for the purpose of this study.
Blood gas analysis	Blood gas analysis is a frequently requested test that can be carried out by utilizing arterial, venous, or capillary whole blood samples. This is particularly true in critical care units and emergency departments, where the procedure is done to evaluate acid-base balance and ventilatory management (Korpi-Steiner, Horowitz, Tesfazghi and Suh-Lailam, 2023).	This definition will be adopted for the purpose of this study.

1.10 Outline of the study

The flow of the thesis is set out as follows:

Chapter 1: An overview and background regarding blood glucose control and dysglycaemia is provided. The research problem and questions, as well as the aims and objectives are highlighted. This is followed by the research design, assumptions, delineation and significance of the study. Key terms and concepts are outlined for clear understanding.

Chapter 2: This is the literature review. This is a detailed discussion and include concepts and definitions. An overview of blood glucose is given, as well as blood glucose homeostasis and its components. A discussion follows about the changes in blood glucose under normal and abnormal physiological conditions. Following this, dysglycaemia and the different components thereof, as well as how critical illness affects each patient is discussed. The role of sepsis in blood glucose control is also discussed.

Chapter 3: This chapter covers the methodology - research design and methods. An overview of why a scoping review is conducted as well as limitations to this method are discussed. The steps in conducting a scoping review are included and outlined.

Since the JBI (Joanna Briggs Institute) methodology for scoping review framework is used, the framework is discussed. The outline for reporting methods according to the PRISMA-Scr guidelines (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) is provided.

Chapter 4: The article submitted for publication is presented, which covers and explains the results of the scoping review.

Chapter 5: This chapter concludes the limitations and recommendations for further research.

Chapter 2: Literature review

2.1 Introduction

Chapter one provided a broad overview of the study and provided the background of the study and that of blood glucose control. In this chapter, an in-depth discussion is provided on blood glucose as the fifth vital sign. An overview of blood glucose is given - followed by glucose homeostasis and its components, as well as its function under normal and critically ill conditions. This chapter gives an overview of dysglycaemia and its components (glycaemic variability, hypoglycaemia, and hyperglycaemia), as well as how it is influenced under critically ill conditions. Different blood glucose monitoring systems in the critically ill population, as well as some available current management strategies are briefly discussed. Since the context is the CCU, the role of sepsis in glucose control is included in this literature review.

2.2 Glucose

Glucose is the main energy source in humans, which is obtained from food. It is a monosaccharide sugar (Gurung, Jialal and Zubair, 2022). Glucose is taken into the body in the form of fructose and galactose, which are monosaccharides and isomers of glucose. These monosaccharides can then combine to form disaccharides for example lactose and sucrose (Gurung et al., 2022). Glucose (from our diet) can be found in the form of polysaccharides such as glycogen and starch – which are large polymers of glucose. Complex sugars are broken down to glucose and fructose to facilitate absorption and metabolism (Gurung et al., 2022).

2.3 Glucose production

Glucose production is discussed in terms of endogenous glucose production under normal physiological conditions as well as during critical illness.

2.3.1 Endogenous glucose production under normal physiological conditions

About 80% of endogenous glucose production takes place in the liver under normal physiological conditions, the other 20% is accounted for by the kidneys (Al-Yousif, Rawal, Jurczak, Mahmud and Shah, 2021). Glucose, fructose, and galactose are the

final products of carbohydrate digestion in the alimentary tract (see figure 1) (Hantzidiamantis and Lappin, 2022).

Glucose is absorbed in the gastro-intestinal tract, following a food bolus, after which it is transported to the liver. Here, glucose is turned into pyruvate to generate adenosine triphosphate or be turned into glycogen. When the body is in a fasting state, the liver plays a role in endogenous glucose production through glycogenolysis and gluconeogenesis (Al-Yousif et al., 2021). Glucose is broken down through anaerobic glycolysis (Hantzidiamantis et al., 2022).

Glucose absorption into the cell is dependent on co-transporters such as sodium (Na+). This Na+-dependent-transport of glucose into the cells make use of the Na+/K+ ATPase pump which generates a negative potential gradient, causing Na+ to move passively into the cell. This action allows glucose to move into the cell against its concentration gradient (Gurung et al., 2022). Consequently, glucose serves as the last common pathway via which all carbohydrates are transported to the tissue cells (Hantzidiamantis et al., 2022).

Glucose is stored in the body as glycogen and is at high concentrations in the liver and muscle tissue (Hantzidiamantis et al., 2022). In glycogenolysis, glycogen is converted to glucose and is released into circulation in a fasted state. It is a short-term solution to increase blood glucose in the circulation in a fasted state. Insulin decreases hepatic endogenous glucose production by promoting glycogen synthesis and inhibiting gluconeogenesis (Al-Yousif et al., 2021).

Gluconeogenesis is a long-term process of endogenous glucose production (Al-Yousif et al., 2021). It is the process whereby the liver and kidney produce glucose in a fasting state (Gurung et al., 2022). Gluconeogenesis is also derived from fat and protein breakdown (Hantzidiamantis et al., 2022). Substrates for gluconeogenesis are lactate, pyruvate, amino acids and glycerol. They exist extra-hepatically and are delivered to hepatocytes or delivered to the liver itself (Al-Yousif et al., 2021). Glucagon promotes gluconeogenic pathways.

The kidneys also contribute to endogenous glucose production, whether in a fed or fasted state, via glucose reabsorption and gluconeogenesis (Al-Yousif et al., 2021). Reabsorption takes place in the proximal tubules of the kidney. Skeletal muscle plays a role in endogenous glucose production by glycogenolysis and is very insulin sensitive (Al-Yousif et al., 2021). Glucose is not released into the bloodstream by muscles but instead, glycogen is converted to glucose for local energy needs (Al-Yousif et al., 2021). Glucose from skeletal muscle must form pyruvate, if not - it is converted to lactate (in the absence of mitochondrial tricarboxylic acid cycle) (Al-Yousif et al., 2021).

The balance between the two hormones glucagon and insulin determines the level of plasma glucose homeostasis (Gurung et al., 2022). Glucagon is released from the alpha cells in the pancreas, whereas insulin is released from the beta cells in the Islet of Langerhans within the pancreas. Insulin – in response to high glucose levels - stimulates glucose absorption into the cells that have glucose transporter type 4 (GLUT-4), which is present in adipose tissue, skeletal and cardiac muscle (Gurung et al., 2022; Hantzidiamantis et al., 2022). Insulin binds to insulin receptors, which has tyrosine kinase activity – and then activates events starting with insulin substrate-1 (IRS-1), culminating in the increased presence of GLUT-4. These insulin receptors are increased in a fasting or starvation state (Gurung et al., 2022).

The body thus maintains its glucose concentrations through balance between glucose uptake and endogenous glucose production (Li, Jia, Ma, Feng, Yu and Du, 2022). A euglycaemic state is necessary to regulate energy homeostasis and plays a vital role in good health (MacDonald, Yang, Cruz, Beall and Ellacott, 2021).

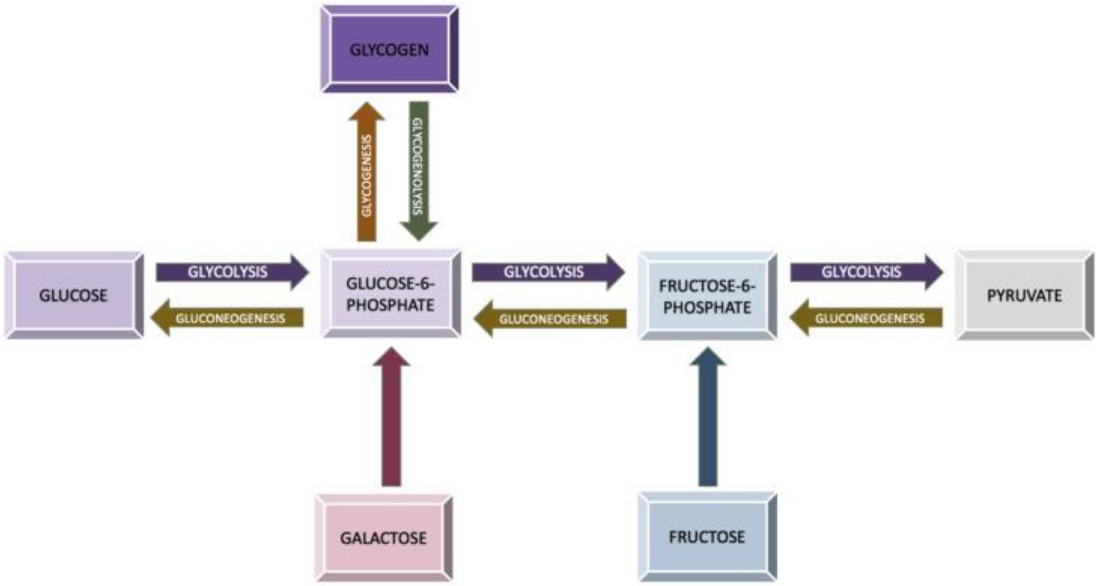


Figure 1: Diagram of the relationship between the processes of carbohydrate metabolism, including glycolysis, gluconeogenesis, glycogenesis, glycogenolysis, fructose metabolism, and galactose metabolism.

2.3.2 Endogenous glucose production in critical illness

Modulation of neural signals, counterregulatory hormone release, pro-inflammatory cytokines, insulin sensitivity and glucose metabolism are all part of the complex process that causes alteration of endogenous glucose production in critical illness (Al-Yousif et al., 2021). It contributes to both hypo- and hyperglycaemia. During critical illness, endogenous glucose production changes according to certain phases and involves factors like cardiac output, energy expenditure and insulin- and cortisol levels (Al-Yousif et al., 2021). These variables change over a period (from admission up to approximately 12 months) depending on what phase the patient is in during critical illness. Catecholamines and systemic inflammation promote gluconeogenesis and glycogenolysis (Al-Yousif et al., 2021).

Glycogenolysis is sustained by the influence of epinephrine and cortisol (Al-Yousif et al., 2021). Gluconeogenesis is mainly stimulated by glucagon, and to a lesser extent epinephrine and cortisol. Insulin levels are increased during day 7-10 post injury/insult, which may lead to hypoglycemia. Endogenous glucose production is reduced in the first 12-24 hours post injury/insult, leading to hypoglycemia (Al-Yousif et al., 2021).

2.4 Dysglycaemia

Dysglycaemia is a common phenomenon in critically ill patients (Joshi et al., 2022; Tickoo, 2019) and comprises of hypoglycaemia, hyperglycaemia, and glycaemic variability. Even though it is common in critically ill patients, it also presents in the non-diabetic patient (Joshi et al., 2022).

As stated, blood glucose is reported in different ways using different metrics: hypoglycaemia, hyperglycaemia, and glycaemic variability. Any disturbance in one or more of these components leads to an increase in mortality (Deane, Plummer and Ali Abdelhamid, 2022; Klonoff, Wang, Rodbard, Kohn, Li, Liepmann et al., 2022).

At microscopic level dysglycaemia has been shown to be linked to endothelial dysfunction and decreased neutrophil chemotaxis. In turn, this may lead to infections, wound complications, and increase length of hospital stay and cost (Canseco, Chang, Karamian, Nicholson, Patel, Shenoy et al., 2022). Uncontrolled blood glucose in the CCU may lead to elevated healthcare costs, as well as high morbidity and mortality (Fortmann et al., 2020).

Critically ill patients often present with dysglycaemia, which is due to disturbed metabolic homeostasis, nutritional intervention, and medications (Fujishima, Gando, Saitoh, Kushimoto, Ogura, Abe et al., 2021). It is believed that adequate glycemic control reduces systemic inflammation, acute kidney injury, and the need for renal replacement therapy, as well as a reduction in the force of the catabolic effect of stress-induced hyperglycemia (Al-Yousif et al., 2021). Numerous factors such as excessive glucose administration, altered insulin release and resistance, stress and other hormonal changes, medication-induced changes and the stress response related to injury or surgery, can all contribute to aberrant glucose homeostasis during the perioperative period (Long and Coursin, 2020).

Abnormal glucose levels adversely affect cerebral ischemia due to endothelial dysfunction, increased oxidative stress, inflammation with release of pro-inflammatory cytokines, apoptosis, and exacerbation of cytotoxic oedema (Kim, Lee, Park and Ko, 2021). Damage to the blood brain barrier in the case of dysglycaemia, has been found to increase the risk of haemorrhagic transformation and worsens the degree

of haemorrhage after reperfusion (Kim et al., 2021). This is seen in patients undergoing endovascular recanalization therapy following ischemic stroke. In studies done by Uyttendaele, Dickson, Shaw, Desaive and Chase (2017); Chase, Desaive, Bohe, Cnop, De Block, Gunst et al. (2018), they found that an increase in mortality is caused by altered glycaemia rather than the underlying patient's metabolic condition, hence glucose control is crucial.

2.4.1 Glycaemic variability

Glycaemic variability defines short-term fluctuations in blood glucose levels secondary to disturbed physiologic endocrine autoregulation (Canseco et al., 2022). Greater rates of reoperation and/or readmission, surgical site infections, and increased mortality has been linked to high glycaemic variability. If glycaemic variability is high during the post-operative period, the likelihood of surgical site infections and readmission within 90 days, remains significantly higher (Canseco et al., 2022).

Glycaemic variability is also defined as the tendency of a patient to experience fluctuations in plasma glucose over a short period of time that are higher than what is expected for a normal physiological response (Tickoo, 2019). Measures of glycaemic variability include, but are not limited to, the amplitude of glycaemic fluctuations over a particular time period in respect to mean plasma glucose and the frequency with which a critical value is surpassed at any given time (Tickoo, 2019).

Mortality is increased in patients with high glycaemic variability, compared to those with average blood glucose values (Tickoo, 2019). In a study by Bagshaw, Bellomo, Jacka, Egi, Hart and George (2009); Tickoo (2019), glycaemic variability was shown to be related to higher probabilities of critical care and hospital mortality when compared with hypoglycemia.

Increased oxidative stress, endothelial dysfunction and cellular apoptosis have been linked to blood glucose fluctuations (Tickoo, 2019; Canseco et al., 2022). Studies have also shown that glucose fluctuations, when compared to sustained hyperglycemia, has a greater impact as a source of oxidative stress (Tickoo, 2019; Mörgeli, Wollersheim, Engelhardt, Grunow, Lachmann, Carbon et al., 2021). Hyperactive inflammatory cells

cause increased endothelial dysfunction, and the effect thereof is worsened if the variability is increased (Tickoo, 2019).

When compared to persistently increased blood glucose levels, fluctuating glucose has a greater detrimental impact on endothelial function and oxidative stress in brain tissues. This results in metabolic dysregulation and secondary brain injury by accelerating microvascular injury (Kim et al., 2021).

Furthermore, compared to non-critical illness myopathy patients, critical illness myopathy patients have been demonstrated to have a significantly decreased level of insulin sensitivity (Mörgeli et al., 2021). Starting on the fifth day of the CCU stay, after the establishment of critical illness myopathy, increased glucose variability with impaired glucose homeostasis could be observed (Mörgeli et al., 2021).

2.4.2 Hypoglycaemia

Blood glucose levels <3.8mmol/L are considered hypoglycaemia, whereas levels <2.2mmol/L are categorized as severe hypoglycemia (Tickoo, 2019). Hypoglycaemia is a strong predictor of increased mortality and morbidity in the CCU (Salinas and Mendez, 2019). Cardiac arrythmias, cardiac ischemia, seizures, and brain damage are all associated with inpatient hypoglycaemia. Neurologic and ischemic complications are strongly associated with inpatient hypoglycaemia (Switzer, Schellenberg, Lewis, Owattanapanich, Lam and Inaba, 2021).

As a result of the NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) trial, blood glucose values are targeted between 7.7-10mmol/L (Switzer et al., 2021). This was a randomized controlled trial, which demonstrated no benefit of strict glycaemic control (4.5-6.0mmol/L) when compared to less tight values of 7.7-10mmol/L. With this standard in place, there were less incidences of hypoglycaemia reported in the CCU (1.5%). When blood glucose ranged between 4.5-6.0mmol/L, the incidence for hypoglycaemia was 5% (Switzer et al., 2021). A meta-analysis showed that patients receiving tight glycaemic control had a fivefold increased incidence of hypoglycaemia (Tickoo, 2019; Yamada, Shojima, Hara, Noma, Yamauchi and Kadowaki, 2017).

Patients undergoing surgical procedures are required to be nil per mouth for prolonged periods of time, thus making hypoglycaemia an iatrogenic cause of hypoglycaemia (Switzer et al., 2021). The study has shown that no mortalities have been associated with iatrogenic hypoglycaemia, which supports the concept that spontaneous hypoglycaemia is more fatal than iatrogenic hypoglycaemia (Switzer et al., 2021).

Patients admitted with polytrauma, cirrhosis of the liver, multi-organ failure, skin, and soft tissue infections as well as necrotizing fasciitis, have been associated with an increased risk for hypoglycaemia (Switzer et al., 2021).

Because the liver is so crucial to glucose metabolism, hypoglycaemia may result from the liver's diminished capacity to raise plasma glucose through gluconeogenesis (Kushimoto, Abe, Ogura, Shiraishi, Saitoh, Fujishima et al., 2020). A study done in the Netherlands indicated that the highest mortality rate for CCU patients was linked to low glucose levels paired with high lactate levels (Chen, Bi, Zhang, Du, Ren, Wei et al., 2019).

Other risk factors for hypoglycaemia include the use of bicarb-containing fluids in patients with continuous veno-venous haemofiltration, interruption of nutritional support as well as sepsis (Tickoo, 2019). Earlier studies suggest that spontaneous hypoglycaemia in the CCU predicted worse outcomes in patients with advanced illnesses such as adrenal insufficiency, renal failure, and liver failure (Tickoo, 2019). More recent research, however, is beginning to recognize that iatrogenic or medication-induced hypoglycaemia is equally dangerous in the critically ill patient (Tickoo, 2019).

Hypoglycaemia is associated with worsened outcomes, but the mechanism thereof, however, remains unclear (Tickoo, 2019). In addition to a state of energy failure, profound and prolonged hypoglycaemia is linked to the release of excitatory neurotransmitters that result in damage and death of neuronal cells because they require energy. In critical illness, acute kidney injury has been associated with hypoglycaemia. Insulin is metabolized by the kidney, resulting in a/the prolonged half-life of insulin in the case where kidney function is reduced, leading to hypoglycaemic events (Al-Yousif et al., 2021).

Arrythmias, ventricular repolarization abnormalities and prolonged QT times may occur during nocturnal hypoglycaemia (Tickoo, 2019).

Although the reasons and connections between hypoglycaemia and the severity of the disease in septic patients are still unclear, inflammatory cytokines, which both enhance glucose utilization and block gluconeogenesis, may be implicated. In other words, hypoglycaemia can be a phenotype that indicates a disordered acute stress response (Kushimoto et al., 2020).

2.4.3 Hyperglycaemia

Hyperglycaemia can be classified as mild hyperglycaemia (blood glucose level of 7.8-10mmol/L) and severe hyperglycaemia (blood glucose level of more than 10mmol/L) (Mitsuyama, Shimizu, Komukai, Hirayama, Takegawa, Ebihara et al., 2022). The occurrence of hyperglycaemia in the critically ill population is as high as 90% (Alotair, Aldasoqi, Baldove and Abdou, 2019; Van Steen, Rijkenberg, Limpens, Van der Voort, Hermanides and DeVries, 2017). Critically ill patients in a surgery CCU had at least one recording of blood glucose more than 11mmol/L, which accounts for about 12% of patients (Wong, Tran and Tsu, 2021).

Hyperglycaemia in critical illness is due to the complex interaction of multiple feedback loops due to inflammation caused by the immune response, counterregulatory response or high blood glucose itself (Chase et al., 2018). These high levels of blood glucose are worsened by unsuppressed endogenous glucose production, medications such as steroids or catecholamines, and exogenously administered nutrition such as total enteral nutrition (Chase et al., 2018).

Pancreatic function is deranged in critical illness and shows similarities to Diabetes Mellitus type 2- namely decreased insulin sensitivity and insufficient secretion (Chase et al., 2018). Insulin clearance is also decreased in the critically ill patient (Chase et al., 2018). Hepatic glucose production is not fully supressed, and insulin is not supplied by the pancreas; resulting in reduced insulin-mediated glucose uptake (Chase et al., 2018).

During acute critical illness, cortisol is released from the adrenal cortex which increases endogenous glucose production and potentiates the action of glucagon (Al-Yousif et al.,

2021). The stress response activates the sympathetic nervous system, which enhances the counterregulatory hormones and catecholamines, increasing endogenous glucose production (Al-Yousif et al., 2021).

Pro-inflammatory cytokines are secreted by immune cells as well as cells in the liver, intestines, and the lungs (Al-Yousif et al., 2021). These cytokines such as interleukin and tumor-necrosis factor, induce insulin resistance, which alters counterregulatory hormone release (Al-Yousif et al., 2021). The actions of endogenous and exogenous insulin have a particularly poor response in septic individuals. These underlying mechanisms of insulin resistance are very complex. Under normal physiological conditions, when an individual is hyperglycaemic, insulin release is induced (β-cells in the pancreas are very sensitive to glucose stimulus) (Al-Yousif et al., 2021). This compensatory mechanism fails in critical illness (Al-Yousif et al., 2021).

Some other effects of hyperglycaemia include a depressed immune system, osmotic diuresis together with electrolyte abnormalities, thinning of skeletal muscles and an increased risk for infections (Al-Yousif et al., 2021). Abnormally high endogenous glucose production may be exacerbated using exogenous nutrition, presenting with an acute kidney injury as well as through glucocorticoid administration (Al-Yousif et al., 2021).

Stress hyperglycaemia, also known as transient hyperglycaemia (blood glucose level > 10mmol/L, in patients not known to have pre-existing diabetes), is very common in the initial 48 hours of illness/injury. Stress hyperglycaemia has a high incidence rate (about 50-80%) in severe illness (Tickoo, 2019). Stress hyperglycaemia is characterized by insulin resistance (Tickoo, 2019).

Mitochondrial toxicity due to hyperglycaemia is linked to multi-organ failure (Tickoo, 2019). Damaged mitochondria are effectively removed via mitophagy and is shown to improve outcomes in critical illness, but this process is worsened by hyperglycaemia and ultimately contributes to poorer outcomes (Tickoo, 2019). The incidence of hyperglycaemia in the CCU is increased by iatrogenic factors such as continuous nutrition, dextrose-containing fluid, exogenous steroids and catecholamines (Tickoo, 2019).

2.5 Blood glucose monitoring and management in the Critical Care Unit (CCU): what is available?

Blood glucose levels should be carefully monitored by healthcare workers in the CCU in order to treat hyperglycaemia, and to limit hypoglycaemia and glycaemic variability (Deane et al., 2022). Thus, the prognosis of critically ill patients depend on dynamic and correct monitoring and treatment of blood glucose levels (Deng, Liu, Pan, Jiang and Li, 2021). Glycaemic control has been shown to reduce CCU patient mortality by up to 45% (Abu-Samah, Knopp, Abdul Razak, Razak, Jamaludin, Mohamad Suhaimi et al., 2019).

Blood glucose monitoring is done using arterial-, venous- or capillary blood (Deane et al., 2022; Salinas et al., 2019). Sample processing is done at the hospital central laboratory (from venous blood), through point-of-care glucose meters (from capillary blood) or blood gas analyzers (using arterial blood) available in most critical care units (Salinas et al., 2019).

According to a study done, blood gas analysis is seen as the “gold standard” in critically ill patients (Eerdekens, Rex and Mesotten, 2020; Deane et al., 2022). This is due to the need for rapid and precise results and the readily available arterial blood gas analyzers in CCU (Deane et al., 2022). The “gold standard” is said to be the central laboratory measurements (Salinas et al., 2019). Venous samples that were sent to the hospital central laboratory were more accurate but is impractical in the CCU environment as insulin titrations need to be done timeously (Salinas et al., 2019). Central laboratory testing is also expensive and time consuming (Deng et al., 2021).

To limit any of the components of dysglycaemia, an ideal monitoring approach would be one that rapidly provides a result, minimizes blood loss (as repeated measurements may be needed), and is precise over a wide range of blood glucose concentrations (Deane et al., 2022).

Using the blood gas analyzer solely to obtain a blood glucose value, without monitoring other variables, may be insufficient and may lead to increased blood loss (due to frequent blood sampling) and environmental waste (Deane et al., 2022). Thus, point-of-care methodologies are utilized in CCU’s using capillary blood. Blood glucose is monitored intermittently using this method and can be obtained quickly, thus making it

ideal in the clinical setting (Deane et al., 2022; Deng et al., 2021). Although measuring blood glucose with a glucometer may seem simple, there is a deviation of 15-20% due to the source of the sample (arterial, capillary, or venous), and variation in operation methods (Deng et al., 2021).

There are, however, discrepancies noted when measuring blood glucose using point-of-care methods/testing vs the so to say “gold standard” measurements. In a study by Deng et al. (2021) it was found that when using two different measurement methods - the blood gas analyzer and a rapid glucometer, the difference in blood glucose values were statistically different. There was a maximum difference value of 2.30mmol/L, which was found to be acceptable in the clinical setting (Deng et al., 2021).

Imprecision with point-of-care testing in critically ill patients might be due to metabolic and cardiovascular abnormalities. Concurrent drug administration results in direct chemical interference, for example ascorbic acid and acetaminophen (Deng et al., 2021; Salinas et al., 2019). Oedema and dehydration are common in the critically ill patient population and is therefore a source of error in point-of-care glucose measurements (Salinas et al., 2019).

It is yet unclear which glucose measuring technique is the most practical, timeous and accurate for critically sick patients to support therapeutic treatment (Deng et al., 2021).

2.6 Sepsis and glucose control

The 2021 Surviving Sepsis Campaign (SSC) Guideline defines sepsis as organ failure brought on by a dysregulated host response to infection. Sepsis is linked to high mortality and has quickly grown to be a major global health burden (Lu, Tao, Sun, Zhang, Jiang, Liu et al., 2022).

In critically ill individuals, especially those with sepsis, the glycometabolism disease is very common (Lu et al., 2022). This disturbance is brought on by stress activation, and it often appears as hyperglycaemia and increased glycaemic variability. Particularly, increased hepatic gluconeogenesis and peripheral insulin resistance during sepsis are caused by the overproduction of pro-inflammatory mediators in response to infections (Lu et al., 2022).

Despite an extensive study to identify the precise mechanisms of the glycometabolism disease, standardized blood glucose management protocols for septic patients have not been developed (Lu et al., 2022). One of the reasons being that the ideal blood glucose target is still up for debate. The protective effect of traditional rigorous glucose management in septic patients has been debunked by numerous multicenter trials, including VISEP (Volume Substitution and Insulin Therapy in Severe Sepsis) and NICE-SUGAR (Brunkhorst, Engel, Bloos, Meier-Hellmann, Ragaller, Weiler et al., 2008; Investigators, 2009).

There are strong connections between the metabolic pathways for lactate and glucose. Since lactate may produce glucose through gluconeogenesis and glucose can produce lactate through glycolysis in the Cori cycle, it is clear that glucose has a significant impact on lactate metabolism and vice versa (Chen et al., 2019). In this regard, blood glucose levels could have a role in the link between elevated lactate levels and a higher risk of mortality in CCU patients (Chen et al., 2019).

2.7 Conclusion

This chapter investigated blood glucose homeostasis and the debilitating effect of dysglycaemia in the critically ill population. Dysglycaemia is a common phenomenon and is also seen in the non-diabetic patient. Increased mortality is associated with the poor management of dysglycaemia. Blood glucose should be managed timeously and effectively to prevent complications. Numerous factors contribute to abnormal blood glucose homeostasis, and if not treated accordingly, may also affect healthcare costs. The importance of monitoring blood glucose is stressed and is a vital prognostic indicator in the critically ill population. Blood glucose management in the critically ill is important to improve patient outcomes as well as reduced length of hospital stay.

Chapter 3: Research design and methods

Scoping review methodology

3.1 Introduction

Chapter 2 discussed definitions, concepts, and physiology regarding blood glucose and its components, as well as several factors affecting blood glucose. In this chapter, the methods used to gather information to answer the research question: how is dysglycaemia managed in critically ill adult patients in the critical care unit? is discussed. For the purpose of the study, the scoping review as a study design will be defined and discussed. The rationale and steps taken in conducting a scoping review as well as the framework and limitations thereof, are discussed.

3.2 Definition

According to the Canadian Institutes of Health Research scoping reviews are exploratory efforts that methodically map the literature available on a topic, finding significant concepts, theories, sources of evidence, and gaps in the study (Peters, Marnie, Tricco, Pollock, Munn, Alexander et al., 2020; Lockwood and Tricco, 2020). Englert et al. (2019) add that scoping reviews are used to map a body of diverse literature already in existence to describe the breadth, depth, and type of research activity within a particular area.

The extent of a body of evidence in a specific area can be determined through mapping. Data about participant groups, study methodology, and study sites are all particularly well-suited for data collection through mapping (Khalil, Peters, Tricco, Pollock, Alexander, McInerney et al., 2021).

Scoping reviews tend to explore topics like “what has been done previously?” or “what does the literature say?” regarding a particular topic (Khalil et al., 2021). Scoping reviews are a review type of the larger family of evidence synthesis and they are becoming more prevalent in many different fields (Munn, Pollock, Khalil, Alexander, McLnerney, Godfrey et al., 2022). Evidence synthesis is described as "the review of what is known from existing research using systematic and explicit methods in order to clarify the evidence base" (Munn et al., 2022:951). It is essential for knowledge

translation and for ensuring that decisions are supported by the strongest evidence possible (Munn et al., 2022).

Scoping reviews enable the reviewers to determine the scope and extent of something being done or used in relation to the review topic (Khalil et al., 2021). A scoping review is a specific type of systematic review and is used to “map rapidly the key concepts underpinning a research area and the main sources and type of evidence available, and can be undertaken as stand-alone projects in their own rights, especially where an area is complex or has not been reviewed comprehensively before” (Englert et al., 2019:5).

An element in which a scoping review differs from a systematic review is that it aims to address more general research questions and to explain ideas and knowledge gaps in a frequently developing topic as opposed to evaluating the efficacy and safety of therapies (McGowan, Straus, Moher, Langlois, O'Brien, Horsley et al., 2020).

3.3 Rationale for conducting this scoping review

It is recommended that extensive glucose management and monitoring be put into place, glycaemic control protocols should be followed, and glucose testing should be completed promptly to prevent hyperglycaemia or hypoglycaemia (See, 2021). A scoping review was chosen for this study because the researcher wanted to explore what evidence is available in the management of dysglycaemia. Gaps in the literature and within practice areas can then be explored to guide clinical practice and the development of glycaemic protocols.

3.4 Indications for using a scoping review

A scoping review's objective is to give a broad overview of the research evidence that is currently available without coming up with a concise answer to a specific research question (Sucharew and Macaluso, 2019; Lockwood et al., 2020). It can be helpful in providing answers to broad questions like "What information has been presented on this topic in the literature?" and for obtaining information and evaluating it before conducting a systematic review (Sucharew et al., 2019:416). Results of a scoping review typically focus on the breadth of recognized content, and quantitative

assessment is often constrained to a count of the sources covering a given issue or recommendation (Sucharew et al., 2019).

The scoping review can be used to guide future research priorities or to enlighten readers about the status of the evidence for a practice area or an emerging topic (Lockwood et al., 2020). Scoping reviews have also been used to identify social determinants of health, as well as to highlight strengths and weaknesses in fields of research (Lockwood et al., 2020).

Along with the growth in primary research output, evidence syntheses (reviews) have also grown in frequency and complexity over time (Peters et al., 2020). The scoping review, sometimes called a "mapping review" or "scoping study," is a method of synthesizing the available evidence that is increasingly used internationally (Peters et al., 2020). Although it is unclear when the first scoping review was conducted, the first methodological guide for these reviews was published by Arksey and O'Malley in 2005. When scoping studies first appeared in the literature, Arksey and O'Malley studied them, thought about them, and offered a ground-breaking framework for their execution. They also recognized parallels and a lack of uniformity (Peters et al., 2020; Tricco, Lillie, Zarin, O'Brien, Colquhoun, Kastner et al., 2016).

A Scoping Review Methodology Group comprised of members of JBI (Joanna Briggs Institute) and the JBI Collaboration (JBIC) was established in 2014 by the JBI International Scientific Committee (Peters et al., 2020). The guidance for scoping reviews specifically addressed the requirement that they be carefully done, transparent, and reliable, just as the guidance for the more conventional systematic reviews, for which JBI is renowned.

The objective of the review must coincide with the review's indication or purpose when using a scoping review approach (Sucharew et al., 2019). Scoping reviews do not undertake a risk of bias assessment of the included evidence, therefore, no assurance of the quality of the included evidence underpinning the results can be made (Khalil et al., 2021). Without a risk of bias assessment, clinical recommendations cannot be graded on the verity of those findings (Khalil et al., 2021).

3.5 Limitations of scoping reviews as methodology

Scoping reviews frequently collect data using a variety of study designs and methodologies without officially evaluating the quality of the evidence (Sucharew et al., 2019). By design, a large amount of research may be included in the review process. As a result, screening large numbers of papers and other sources for possible inclusion in the scoping review often requires a big study team (Sucharew et al., 2019).

Because scoping reviews give a descriptive representation of the information that is available, this frequently results in broad, less specific searches that call for numerous organized techniques centred on different sets of themes. Hand searching the literature is thus essential to validate the process (Sucharew et al., 2019). Due to the extensive search coverage entailed in the approach, scoping reviews take a long time to complete (Sucharew et al., 2019). Scoping reviews are susceptible to bias from several sources, much like other studies. Although it is not seen as necessary, some scoping reviews may include an evaluation of the possibility of bias (Sucharew et al., 2019). Bias may not be formally evaluated, but that does not mean it does not exist (Sucharew et al., 2019). For instance, selection bias may arise if the scoping review does not identify all data that are accessible on a topic and the subsequent descriptive account of the information that is available is inaccurate (Sucharew et al., 2019).

3.6 Framework of scoping reviews

Scoping reviews should be carefully prepared and guided by a protocol, as is characteristic of rigorous evidence synthesis methodologies (Peters et al., 2020). In 2005, Arksey and O'Malley produced the first scoping review framework (Arksey and O'Malley, 2005). The authors gave a general outline of a scoping review, but they did not provide any specific methodological instructions on how to carry one out (Khalil et al., 2021). This was followed by a contribution from Levac and colleagues (2010)(Levac, Colquhoun and O'Brien, 2010), who updated the framework and reflected upon the idea put forth by Arksey and O'Malley (Khalil et al., 2021). A methodological group was established by the JBI (Joanna Briggs Institute) in 2013 to create clear, thorough, and precise guidelines for conducting scoping reviews, with the latest updated guideline being in 2020 (Khalil et al., 2021). Like a systematic review, a scoping review needs a well-defined research question, without it, the reviewers

might extract information that has nothing to do with the question (Khalil et al., 2021). The researcher used the JBI methodology as set out by (Peters, Godfrey, McInerney, Khalil, Larsen, Marnie et al., 2022).

3.7 JBI recommended steps for conducting a scoping review

3.7.1 Eligibility criteria

These criteria are used to determine what is included in the review and what is excluded, based on the review's aim and questions (Peters et al., 2022). The PCC (participant, concept, context) framework used to create the research objective(s) and question(s) guides the inclusion and exclusion criteria, informing the literature search strategy (Pollock, Davies, Peters, Tricco, Alexander, McInerney et al., 2021). Exclusion criteria are followed by a reason as to why it is excluded (Pollock et al., 2021).

The articles that have been reviewed were determined by eligibility (which studies to be included or not) standards (Pollock et al., 2021). Ambiguous eligibility standards may cause the inclusion of too many papers or that no suitable papers are found (Pollock et al., 2021). Eligibility criteria are outlined in table 1, and elaborated more on page 37.

Participants

This component is occasionally referred to as "population." Important participant characteristics from potentially relevant sources of evidence, such as age, diagnosis, role (e.g., nursing staff), and any additional qualifying criteria that make a specific participant group appropriate for the scoping review's objective and questions, should be clearly described (Peters et al., 2022). Enough information should be provided so that the authors are able to easily and unequivocally identify participants who are eligible for inclusion and those that are excluded (Peters et al., 2022). Participants should be included or excluded with good reason, as stated.

Concept

The main problem or subject that the scoping review will investigate is the concept (Peters et al., 2022). Definitions, methodological techniques, study design, theories, interventions, programs, and conduct decisions could all be included in this category. The concept of the proposed review could also be referred to as the focus of the scoping review, which often contains information crucial to the review's goal and key questions (Peters et al., 2022). This could include information about the interventions (such as surgical techniques, pharmaceutical and/or non-pharmacological therapies), phenomena of interest (such as participant experiences or perspectives), and/or outcomes (such as quality of life, and patient-reported outcomes). The types of methodologies, theoretical models, procedures, and approaches that will be investigated may be revealed in the concept (Peters et al., 2022).

Context

The context element of a scoping review's eligibility criteria typically has to do with the concept's field, location, and/or review participants (Peters et al., 2022). The term "context" can refer to the setting in which the sources of evidence (in this case, studies) were used, such as primary healthcare settings including hospitals, general practices, and specialized medical facilities (Peters et al., 2022). Additionally, context can refer to a country or region's geographic location (for example, low- to middle-income nations or rural, isolated locations). The context component may also take timing into account (e.g., within the framework of recent medical practice during the last five years, preoperative circumstances, within the context of gender empowerment research over the past 30 years) (Peters et al., 2022).

Table 1: Eligibility criteria according to the PCC framework

Variable	Description	Inclusion criteria	Exclusion criteria
Population	Adult patients managed in critical care units where blood glucose monitoring was done	(i) patients 18 years or older, (ii) female and male patients, (iii) patients of any race and ethnicity, (iv) patient admitted to the critical care unit following a medical or surgical diagnosis, (v) studies from 2001	(i) persons under the age of 18 years, (ii) patients with a pre-existing history of Diabetes Mellitus, (iii) patients on a protocol for glycaemic management for Diabetes Mellitus (DM) and (iv) studies prior to 2001
Concept	Evidence of management (assessment, diagnosis, implementation, and evaluation) of dysglycaemia in patients in CCU this includes the method of sampling blood glucose, frequency, method of Insulin or dextrose administration, evaluation of blood glucose	1. Sampling method of blood glucose 2. Frequency monitored. 3. Target range of blood glucose guiding treatment (hypo or hyper) 4. Method of Insulin or Dextrose administration 5. Evaluation	Patients with DM
Context	The critical care unit	Intensive care units and high care units.	Studies conducted outside of the critical care unit.

3.7.2 Types of evidence sources

Evidence sources for a scoping review can be any literature for example, primary studies, systematic reviews, meta-analyses, letters to the editor, guidelines, websites, and policy papers (Peters et al., 2022). To allow for the inclusion of all sources, authors may opt to leave the source of the information open. Otherwise, restrictions may be imposed on the kinds of sources that are acceptable (Peters et al., 2022). Due to the inclusion of both primary sources and evidence syntheses that have the primary source, authors conducting scoping reviews are likely to run into instances where duplicate data is discovered, here, it is advised that the authors openly describe how they would deal with this situation while doing their review (Peters et al., 2022).

For this review, all research articles was included. Case reports as well as editorial letters, opinion papers and surveys were excluded. Systematic review papers were excluded. Only papers published in English was included.

3.7.3 Search strategy

The process of seeking sources to include in the scoping review relies on a suitable variety of relevant keywords and concepts/terms (Peters et al., 2022). Choosing the

right keywords and concepts might be difficult because different sources use different terminology, and adapting search algorithms for various datasets with various taxonomies and indexing terms can make this more challenging (Peters et al., 2022). During this phase, the intention is to locate all pertinent published and perhaps unpublished evidence (Pollock et al., 2021).

Detail regarding the search strategy should be provided, including whether a preliminary search will be conducted across a small number of databases. It is done to identify potentially pertinent keywords and terms for developing a final search strategy across all databases. Information should also be provided whether the reference lists of pertinent sources of evidence will be checked for additional references, and whether important authors will be contacted (Peters et al., 2022).

A variety of relevant databases should be searched for the evidence. These may include the Medline, CINAHL, or OVID, EMCare, Cochrane, Joanna Briggs Institute EBP, and Nursing and Allied Health databases for nursing and midwifery (Pollock et al., 2021). The search strategy should be implemented in three steps, working along with an information specialist (Pollock et al., 2021).

Initial search:
To guide the final search strategy, conduct an initial search for publications pertaining to the review topic in at least two relevant databases. Look for words and phrases in the title, abstract, and index of papers that would probably be covered in the review (Pollock et al., 2021).

Second search:
A formal search will be conducted in the chosen databases and grey literature (if included) using the search terms that have been identified. These searches must be recorded so that they can be used in the final Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (Pollock et al., 2021).

Reference list search:
The reference list of articles is then searched for (a) all identified studies from the original search, (b) studies from the full-text review, or (c) studies from the review (Pollock et al., 2021). The Peer Review of Electronic Search Strategies (PRESS)

checklist is a valuable tool for assessing the search strategy (Pollock et al., 2021). During this stage, the title of the articles is analysed and assessed whether it aligns with the review inclusion criteria. Details of how many studies were identified in the reference list search is then included in the PRISMA flow chart (Pollock et al., 2021).

The databases searched in this scoping review were Medline and CINAHL. Articles that were published from 2001 until present was evaluated and the search was limited to articles published in English. We used the following search terms: (*Glucose monitoring OR glucose control OR glycaemic control OR dysglycaemia), NOT (Diabetes mellitus OR Diabetes OR Diabetic), AND (Critically ill OR intensive care patients OR critical care patients).* Research articles was included. Case reports as well as editorial letters, opinion papers, and surveys were excluded.

3.7.4 Evidence selection

A source of evidence is chosen purely based on whether it meets the protocol's inclusion or eligibility criteria after the search (Peters et al., 2022; Pollock et al., 2021). The identified sources of evidence are screened, first at the level of the title and/or abstract, then looking at sources that seem relevant in full text (Peters et al., 2022). The researcher and supervisor screen and choose the evidence sources, (e.g., two or more people screening/selecting all or a subset of potentially relevant sources to assess agreement) (Peters et al., 2022). There should be consistency between authors and what they choose. Thus, a declaration about how disagreements will be handled should be mentioned. Disagreements are typically resolved through discussion between the two data screeners or by involving a third party to decide (Peters et al., 2022).

The PRISMA flowchart (Figure 2) provides the detail of the search yield and. All identified studies were exported to “Rayyan”, a web-based tool which assists in the process of screening and selecting studies. Duplicates were removed and abstracts and titles were screened for inclusion criteria. Where uncertainty existed in the screening of only titles and abstracts – full texts were screened. The bibliographies of included articles were then manually searched for additional articles which were

eligible. Two of the authors reviewed the examined the articles (title/abstract/full text) and no discrepancies needed resolving.

3.7.5 Data extraction

Evidence can be extracted from sources after they have been selected for inclusion (Pollock et al., 2021). The objective of extracting the evidence is to summarize the scoping review's findings clearly and simply (Peters et al., 2022). In addition to obtaining basic descriptive information about the sources of evidence that were used, such as the authors, titles, and year of publication, the data to be extracted should also be in line with the review question(s) and the inclusion criteria (Peters et al., 2022).

Before data are formally extracted, two stages should take place. The first step is when a standard extraction form is created during the protocol development stage (Pollock et al., 2021). Secondly, the extraction form should be pilot tested with two or more reviewers and two to three manuscripts, to ensure consistency (Pollock et al., 2021). This may be an ongoing process in scoping reviews, and the form may be changed (Pollock et al., 2021).

All data were extracted by one author, using an Excel spreadsheet. A second author verified and validated the data. Further details such as author, year of publication, country of publication, as well as the objective of the study, were added. Through this extraction (Table 2), it was possible to perform the synthesis, data interpretation, and analysis presented in this review. For this review, a narrative synthesis was performed to describe the study details and findings, to answer the question posed.

3.7.6 Data analysis

Scoping reviews don't aim to produce a set of final estimates or findings to guide decision-making; rather, they aim to give a map and summary of the evidence that is already available. Therefore, the analysis of the data acquired from the included research is typically descriptive, using methods like frequency counting and basic coding (Pollock et al., 2021). It should include information on the methodology the review authors plan to analyse, summarize, and present all the sources cited in the review as well as the data extracted from them (Peters et al., 2022). Data analysis

in scoping reviews is typically descriptive, with the most common methods being basic frequency analysis and percentages (Peters et al., 2022).

3.7.7 Presentation of the results

Maps, graphs, and tables are used to display the results (Peters et al., 2022). Tabular format is mostly used to present results from a scoping review (Pollock et al., 2021). The elements of the PCC mnemonic and other pertinent data that is consistent with the study's goals and research question, should be included in these tables (Pollock et al., 2021).

Reviewers appear to find it difficult to present the results in a scoping review, and a clear presentation may call for some meticulous planning and original thinking (Khalil et al., 2021). Tables are helpful for connecting ideas related to the review topic, but it is also feasible to display independent variables in a new table so that they can be classified or analysed in accordance with recognized classification schemes (Khalil et al., 2021). Another method of demonstrating the evolution of knowledge over time and the rising awareness of specific concepts is to use gap maps (Khalil et al., 2021).

The results of this scoping review were presented in text only presentation. A full description of the results was given and outlined. No graphs or charts were used.

3.8 Reporting of scoping reviews

An international team of experts in scoping reviews and evidence synthesis, developed the Preferred Reporting Items for Systematic Reviews extension for Scoping Reviews (PRISMA-ScR) in 2018. It is consistent with JBI's scoping review methodology and gives reviewers a reporting checklist for their reviews (Peters et al., 2020). See Annexure A.

The PRISMA-ScR has two optional elements in addition to the 20 essential items that should be reported (critical appraisal of individual sources and within sources of evidence) (Pollock et al., 2021). To guarantee that a scoping review follows reporting standards, the PRISMA ScR is utilized to help with the development thereof (Pollock et al., 2021).

The EQUATOR (Enhancing the QUAlity and Transparency Of Health Research) network is an international initiative that was established in 2006 with the goal of enhancing the validity and worth of published health research. It does this by encouraging accurate, thorough, and transparent reporting of all studies, as well as the widespread application of reporting guidelines to support reproducibility and usefulness, and to reduce avoidable research waste (Network, 2019).

The Enhancing the QUAlity and Transparency Of health Research (EQUATOR) Network defined reporting guidelines as, ‘‘a checklist, flow diagram, or structured text to guide authors in reporting a specific type of research, developed using explicit methodology" (McGowan et al., 2020:177) .

Reporting guidelines were created because of observations that numerous published papers omit crucial information regarding the study's objectives, procedures, or findings (Network, 2019). Incomplete reporting (such as omitting participant information or reporting data or results selectively), inaccurate reporting (such as discrepancies between the abstract and the main text, confusing or misleading data or graphs, and the introduction of results), and problems with delayed reporting or non-publication of research studies are common issues found in research publications (Network, 2019).

Following published advice from the EQUATOR Network, the processes in building PRISMA-ScR included rigorous and iterative approaches, including a modified Delphi and a 24-member expert, worldwide face-to-face panel with two research leads. The resulting PRISMA-ScR checklist consists of two optional items in addition to the 20 mandatory minimum reporting elements (McGowan et al., 2020). By operating an open access portal that compiles reporting guidelines and those under development, the EQUATOR Network has coordinated a global effort to address reporting deficiencies across numerous disciplines and fields (McGowan et al., 2020). With the intention of reporting and disseminating their work widely to a variety of consumers, researchers devote a tremendous amount of time writing journal publications (McGowan et al., 2020). A publication must be presented appropriately for customers to read it and act upon it (McGowan et al., 2020).

To help address the concerns of publication record deficiencies, including missing and biased material, reporting guidelines have been created (McGowan et al., 2020). Experts have developed reporting guidelines as knowledge translation tools to help ensure transparency and completeness of reporting with the overall objective of improving the quality and dissemination of health research (McGowan et al., 2020).

The PRISMA-ScR aims to aid readers (researchers, publishers, commissioners, policymakers, health care professionals, guideline creators, and patients or consumers) in better understanding relevant terminology, fundamental ideas, and key items to report for scoping reviews (Tricco, Lillie, Zarin, O'Brien, Colquhoun, Levac et al., 2018).

It has been shown that reporting guidelines promote methodological transparency and the use of research findings by outlining a minimal set of items that should be included in research reports (Tricco et al., 2018).

3.9 Summary

Scoping reviews maps the available literature on as specific topic, finds significant concepts and theories to identify gaps in the literature. It addresses more general research questions and explains ideas and knowledge gaps. Certain criteria are used to screen eligible articles to be included in the study, based on participants, the focus of the review and the setting. To identify what areas in the clinical field needs more in-depth research, a scoping review assists in identifying these areas. Before evidence-based guidelines can be set up, a scoping review must first be conducted to identify what has already been done and how it is done.

Chapter 4: Management strategies of dysglycaemia in critically ill adult patients: A scoping review

This dissertation is intended to be published in the journal: Intensive and Critical Care Nursing. A brief introduction of dysglycaemia is given, followed by study methods as well as the results of the review. Follow the link for the authors guidelines: Guide for authors - Intensive and Critical Care Nursing - ISSN 0964-3397 | ScienceDirect.com by Elsevier.

INTRODUCTION

The presence of glucose is essential to support life and is needed to maintain normal metabolic processes. Blood glucose is therefore an important part of clinical monitoring, as it is a prognostic parameter (Kesavadev et al., 2021). Metabolic and glucose equilibrium is seen as part of essential functioning, and measuring the serum glucose level is regarded as the fifth vital sign (Fortmann et al., 2020). Critically ill patients are prone to dysglycaemia which comprises of the following domains: hypoglycaemia, hyperglycaemia, and glycaemic variability. Dysglycaemia in critical illness patients is caused by endogenous glucose production and an impaired counterregulatory response. It serves as a biomarker of disease severity and leads to increased mortality in these patients (Aramendi et al., 2017). In addition a variety of drugs used in the intensive care unit (ICU) together with the stress response, contributes to dysglycaemia (Joshi et al., 2022).

The pancreas regulates blood glucose levels by producing a variety of hormones, mainly insulin and glucagon, which keep blood glucose levels within a very specific range (Röder, Wu, Liu and Han, 2016). Glucagon and insulin work in opposition to each other to preserve this balance, a process known as glucose homeostasis (Röder et al., 2016).

Moreover, glucagon induces hepatic and renal gluconeogenesis to boost endogenous blood glucose levels during extended fasting. Glucagon is released from α-cells during sleep or in between meals, when blood glucose levels are low (Röder et al., 2016). Glycogen that has been stored in the liver and muscles may be broken down when blood sugar levels drop (Leszek, 2017), known as glycogenolysis.

On the other hand, postprandial elevations in exogenous glucose promote the release of insulin from β-cells. Insulin causes the insulin-dependent absorption of glucose into muscle and adipose tissue after binding to its receptor in these tissues. This process decreases blood glucose levels by eliminating exogenous glucose from the bloodstream (Leszek, 2017).

Tight glucose control reportedly decreased mortality and morbidity in critically ill patients (Van den Berghe et al., 2001; Krinsley, 2004a). However, the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation [NICE-SUGAR] trial found that tight glucose control increased the risk for hypoglycaemia and that intensive insulin therapy increased mortality (Sreedharan et al., 2022). Therefore, this scoping review was done to explore how dysglycaemia is managed in the critically ill adult patient in critical care units?

METHOD

A scoping review was conducted in accordance with the Joanna Briggs Institute) (JBI) methodology for scoping reviews (Peters et al., 2022; Peters et al., 2020), the protocol was not registered on any platform. Scoping review was chosen as it brings together information from different sources on the particular topic. The approach is exploratory.

Literature search

The databases searched in this scoping review were Medline and CINAHL. Articles that were published from 2001 until 2023 were evaluated and the search was limited

to articles published in English. We used the following search terms: (*Glucose monitoring OR glucose control OR glycaemic control OR dysglycaemia), NOT (Diabetes mellitus OR Diabetes OR Diabetic), AND (Critically ill OR intensive care patients OR critical care patients).* Research articles was included. Case reports as well as editorial letters, opinion papers and surveys were excluded.

Article selection

The PRISMA flowchart (Figure 2) provides the detail of the search yielded. All identified studies were exported to “Rayyan”, a web-based tool which assists in the process of screening and selecting studies. Duplicates were removed and abstracts and titles were screened for inclusion criteria. Where uncertainty existed in the screening of only titles and abstracts – full texts were screened. The bibliographies of included articles were then manually searched for additional articles which were eligible. Two of the authors reviewed the examined articles (title/abstract/full text) and no discrepancies needed resolving.

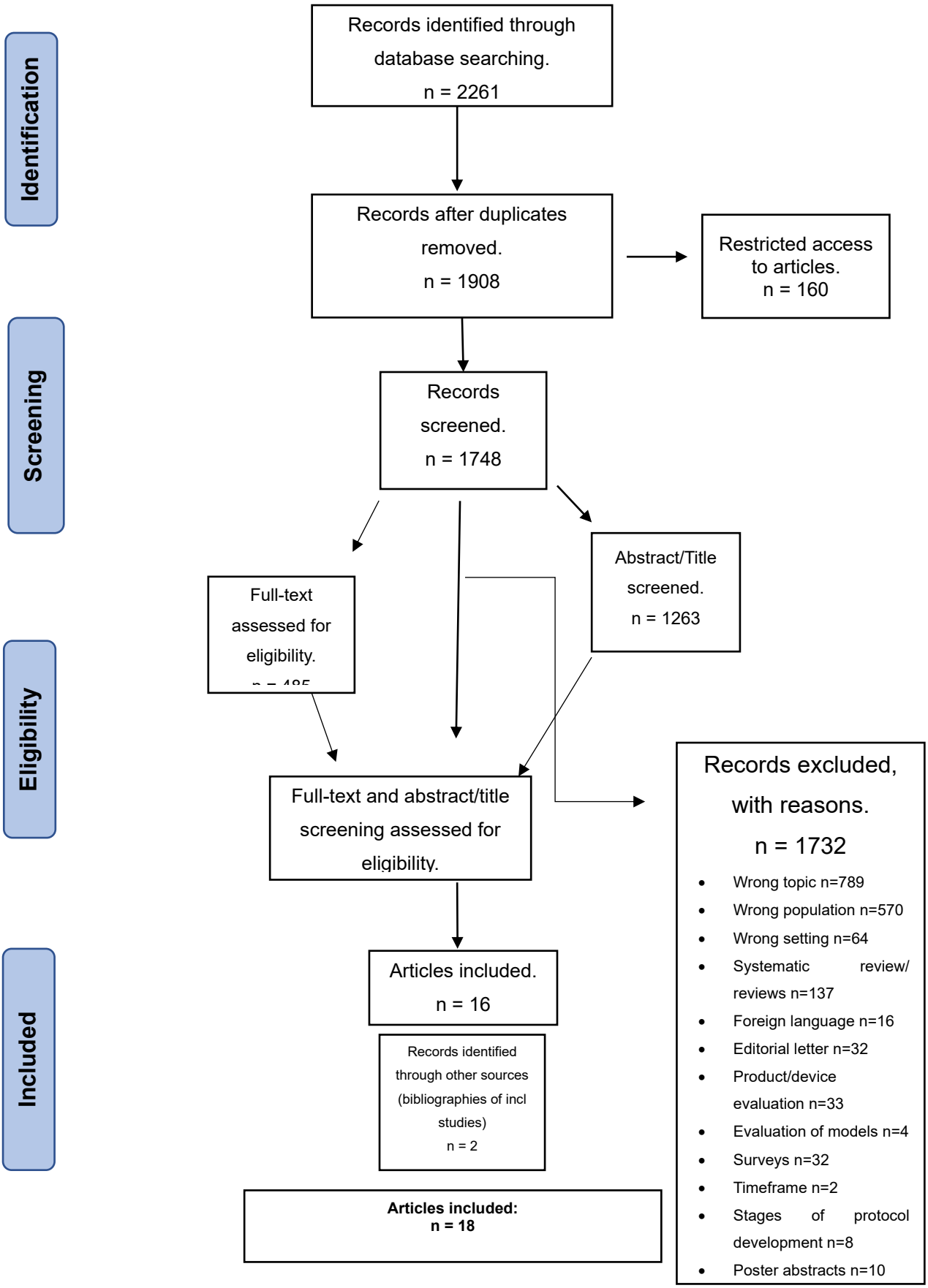


Figure 2: PRISMA flow diagram of included studies.

Eligibility criteria (according to PCC framework)

Studies was included if they met the following criteria: (i) all patients above 18 years of age, (ii) all female and male patients, (iv) any patient admitted to the critical care unit following a medical or surgical diagnosis, (v) any patient requiring blood glucose management during CCU stay and (vi) studies that includes information regarding the topic on hand from the year 2001 up to 2023. This date was chosen because the largest randomized controlled trial was done for the first time in Leuven on glucose control and intensive insulin therapy, and since then studies failed to reach consensus.

Exclusion criteria were as follows: (i) patients already diagnosed with Diabetes Mellitus, (ii) persons under the age of 18 years, (iii) patients on any protocol for glycaemic management for Diabetes Mellitus and (iv) any study discussing the topic on hand prior to the year 2001.

Data charting process

Data was extracted that presented each of the following parameters from the included papers: target range of blood glucose, sampling method of blood glucose, frequency of blood glucose testing, method of insulin or dextrose administration, outcome and results. All data were extracted by one author, using an Excel spreadsheet. A second author verified and validated the data. Further details such as author, year of publication, country of publication, as well as the objective of the study, were added. Through this extraction (*Table 2*), it was possible to perform the synthesis, data interpretation, and analysis presented in this review. For this review, a narrative synthesis was performed to describe the study details and findings, to answer the question posed.

Table 2: Data Extraction

Author/s + country of publication	Objective of study	Population	Target range of blood glucose	Sampling method of blood glucose	Frequency of blood glucose testing	Method of insulin or dextrose administration (i.e., protocol type etc)	Outcomes/ Results
Rodriguez et al. (2022) **Spain**	Analysis of the agreement between arterial, central venous, and capillary blood samples using glucose meter in critically ill patients	A total of 297 measurements from 54 patients were included in the study.		Central venous catheter blood, arterial blood and capillary blood samples were taken.		Subcutaneous insulin was used to treat many patients, accounting for 93% (276) of the measures.	When a glucose meter is used, there is little agreement between arterial, capillary, and central venous samples for blood glucose readings.
Bleck (2006) **Belgium**	To ascertain whether intensive insulin therapy improve neurologic outcomes in critically ill patients.	1548 critically ill ventilated patients.	Intensive insulin therapy group: strict glycaemic control: 4.4and 6.1 mmol/L. Usual care group: commence insulin therapy if blood glucose > 12 mmol/L, maintain blood glucose at 10.0 -11.1mmol/L.				Intensive insulin therapy decreased the likelihood of additional prolonged ventilation and neurologic complications in critically ill patients with isolated brain injury or prolonged ventilation.
Ellis et al. (2013) **Durham**	To compare arterial blood samples using the clinical chemistry lab with capillary and	50 adult post-operative cardiothoracic patients		Capillary and arterial sites. Clinical chemistry laboratory testing (CLT)			Findings demonstrated that the capillary point of care testing produced low and unacceptable agreement levels

	arterial blood samples using pint of care testing in patients following cardiothoracic surgery			and point of care testing (POCT) were used to test the samples.			with the gold standard clinical chemistry lab. Since arterial point of care testing and the clinical chemistry lab's results agreed within a 95% acceptable range, arterial point of care testing is safe for the use of insulin infusions.

Table 2: Data extraction (continued)

Green et al. (2010) **Hawaii**	To ascertain whether maintaining blood glucose levels between 4.4 and 6.1 mmol/L with intensive insulin therapy (IIT) or below 8.3 mmol/L with conventional treatment was linked to a lower rate of mortality and better functional outcomes in critically ill patients.	81 patients	Intensive control group (range of 4.4-6.1mmol/L) *n*=45 Conventional control group (range <8.3mmol/L) (range 4.4-8.3mmol/L) *n*=36	Intensive group: Arterial catheter, or capillary blood (fingerstick). Conventional group: Arterial line or capillary blood (fingerstick). A glucometer was primarily used to measure the level of glucose.	Intensive group: Initially 1hrly, then 2hrly until levels stabilised. Conventional group: Every 6 hrs.	Intensive group: continuous insulin infusion titrated to achieve a target blood sugar level of 4.4–6.1 mmol/L. Conventional group: Start treatment if blood glucose > 8.3 mmol/L. Subcutaneous insulin (sliding scale) for a blood sugar of 8.3-11.1mmol/L.	IIT showed no benefit in this small group of critically ill neurologic patients, as there was no significant difference in mortality, morbidity, ICU length of stay, or functional outcome.
Mann et al. (2011) **Texas**	To ascertain whether serum glucose concentration control in a burn intensive care unit can be achieved safely and effectively with the use of computer decision support software (CDSS).	Standard of care paper protocol (PP) Computer protocol (CP) CP group: *n*=10 PP group: *n*=8	For both standard of care paper protocol (PP) or Computer protocol (CP): 4.4 - 6.1mmol/L:	Point-of-care glucometers was used.	PP group: 2 hrly CP group max. 1 hrly	Insulin therapy were started if two hourly serum glucose measurements were≥ 8.3mmol/L, then hourly blood glucose measurements guided the insulin titration Dextrose were given at values less than 3.8mmol/L	Compared to a conservative paper-based nomogram, CDSS enabled burn ICU patients to achieve target glucose more frequently, improving glycaemic control. There was also no discernible increase in the risk of hypoglycaemic events.
Gibson et al. (2009) **Baltimore**	To ascertain whether strict glyceamic control achieved by intensive insulin therapy (IIT) is	37 patients Surgical ICU - *n=22* Burns ICU - *n=15*	- Tight glycaemic control: average <8.3mmol/L	The measurements of blood glucose obtained from finger sticks, from laboratory values	Until three consecutive glucose readings fall within the desired glucose range of 5-6.6	Yale insulin infusion protocol	Patients on IIT who have strict glyceamic control have lower mortality rates in the Burns ICU

	beneficial for critically ill burn patients.		- Poor glycaemic control: average >8.3mmol/L	obtained from scheduled venous samples, and/or from arterial blood samples taken from an indwelling catheter.	mmol/L without necessitating an adjustment to the insulin infusion, glucose measurement ta ken at least once every hour.		(20% vs.50%) and Surgical ICU (0% vs. 58%). In the Burns ICU, patient survival has been associated with strict glycaemic control, as well as a lower rate of total body surface area burn.

Table 2: Data extraction (continued)

Shearer et al. (2009) **Portland**	To compare the glucose measurements obtained from a point-of-care (POC) device for catheter and fingerstick blood samples with those obtained from clinical laboratory analysis of a catheter blood sample.	The study included 63 critically ill adult patients.		Central venous catheter blood: - for central lab analysis - for POC device Fingerstick (capillary blood) - for POC device			Significant statistical and clinical differences were observed between laboratory and point-of-care glucose readings. Point of care values for fingerstick (capillary) and CVC blood samples did not differ. It is acceptable in critical care units to use both capillary and CVC blood interchangeably when performing point of care testing.
Graffagnino et al. (2010). **USA**	A program of IIT (intensive insulin therapy) to achieve a blood glucose of 4.4-6.6 mmol/L. (p307).	3,709 patients	Standard insulin therapy: Blood glucose level: 8.3mmol/L Intensive insulin therapy: Insulin therapy was titrated to achieve glucose levels between 4.4-6.6mmol/L Moderate hypoglycaemia: <3.8 mmol/L, severe hypoglycaemia as	Capillary blood obtained using a blood glucose monitor via venous or fingerstick sampling.		To maintain the lower glucose set points, adjustments were made to both the continuous insulin drip protocol and the modified multi-dosing insulin protocol.	An increased risk of mortality was linked to hyperglycaemia (> 16.6 mmol/L) in a group of patients suffering from critical illnesses. When glycaemic control was achieved through an intensive insulin strategy (target glucose level 4.4–6.6 mmol/L), the probability of hypoglycaemic episodes increased in comparison to the more conservative standard approach (target glucose <8.3 mmol/L). Any level of hypoglycaemia was linked to a higher death rate.

			<2.2 mmol/L, extreme hypoglycaemia as <1.1 mmol/L Hyperglycaemia: - Blood glucose level > 16.6mmol/L - severe - Blood glucose level of 6.1-8.0 mmol/L - mild				
Staszewski et al. (2011) **Poland**	To determine whether intravenous (IV) insulin treatment is safe and effective in reducing mortality and functional short-term disability in nondiabetic AIS patients with mild hyperlgycaemia by achieving strict glycaemic control.	ISI: intravenous insulin infusion- *n*=26 CG: control group - *n*=24	ISI group: - Blood glucose range: 4.5 – 7 mmol/L. *strict glycaemic control.* CG: - Blood glucose <10mmol/L *(commence treatment if >10mmol/L)*	ISI group: - Capillary blood CG: - Capillary blood	ISI group: - Initially 1hrly until within the targeted range, then decreased to every 4 hrly. CG: - 4hrly	ISI group: - 24-hour IV insulin infusion CG: - Subcutaneous insulin Symptomatic hypoglycaemia was treated with dextrose and blood glucose was rechecked every 15 minutes. If hypoglycaemia persists, protocol treatment was continued.	Intensive 24-hour intravenous insulin therapy is a relatively safe and effective treatment option for non-diabetic patients with mild post-stroke hyperglycaemia. Maintaining blood glucose at 7 mmol/L for the first 24 hours following ictus may lessen neurologic impairment.
Petersen et al. (2008)	The difference between a point-of-care glucose meter	84 patients.	Hypoglycaemia: venous plasma	- Arterial blood - Central venous catheter blood.		For hypoglycaemia: Blood glucose measurements were	Glucose meters can be used in a MICU and have a strong correlation with clinical laboratory

USA	and the main clinical laboratory for medical intensive care unit patients on a strict glycaemic protocol were investigated. Investigated whether the location of blood sampling had a significant impact on glucose values.		glucose <3.9 mmol/L. Clinically significant hypoglycaemia: <2.2 mmol/L.	- Capillary blood (fingerstick). - Point of care meter was used for all 3 sources - Arterial and venous blood - blood gas analyser - Arterial and venous blood collected in blood tubes and sent to main clinical laboratory for testing.		taken every 15 to 30 minutes until the blood glucose reached at least 5.0 mmol/L, and then hourly after that until stabilization. If the blood glucose level was less than 2.2 mmol/L, or at the discretion of the bedside nurse, 25 ml of 50% dextrose was administered intravenously.	instruments that are routinely used.

Table 2: Data extraction (continued)

DuBose et al. (2012) **LA & Southern California**	Examining the accuracy of capillary blood glucose (CBG) in critically ill trauma patients while they are in the shock state in comparison to laboratory blood glucose (LBG).	A total of 1215 patients were admitted to the ICU. This analysis included 1935 CBG and LBG paired samples in total.		- Capillary blood (fingerstick) (CBG) - glucometer - Peripheral, arterial or central venous blood - central laboratory (LBG)			Following trauma, there is little correlation between the laboratory and capillary glucose readings in the shock and non-shock states. Prior to starting treatment, values obtained through capillary glucose sampling techniques should be verified by laboratory measurements.
Kaukonen et al. (2009) **Finland**	To investigate the prevalence of hypoglycaemia and its effect on patients' outcomes.	A total of 1024 patients.	4–6 mmol/L	Arterial blood gas measurement	Measurements were done at 2hrly intervals		In comparison to earlier trials, severe hypoglycaemia during intensive insulin therapy is relatively uncommon in clinical practice. If the advantages of tight glycaemic control can be verified in additional trials, the risk of hypoglycaemia shouldn't prevent the standardized use of intensive insulin therapy.
Thomas et al. (2005) **Salford**	It describes efforts to use a basic web-based insulin dose calculator to improve glycaemic control in critically ill patients.	A total of 891 patients were studied.	Target blood glucose: 5.4 to 7.1 mmol/L.	The use of blood gas analyser and glucometers.	On admission to ICU and then at 08:00 daily by laboratory measurement.	Insulin sliding scales prescribed by the resident medical staff are used to control blood glucose.	We have shown that using an insulin calculator improved glycaemic control in an intensive care unit (ICU) outside of a research setting.

Table 2: Data extraction (continued)

Griesdale et al. (2009) **Canada**	The relationship between serum glucose levels and mortality in individuals with severe traumatic brain injury, were examined. The association between the risk of hypo- and hyperlgycaemia episodes and mortality were examined.	170 patients.	Maintain blood glucose <10 mmol/L Hyperglycaemia: blood glucose ≥ 11.1 mmol/L. Hypoglycaemia and severe hypoglycaemia: blood glucose ≤ 4.4 mmol/L and ≤ 2.2 mmol/L.		Monitor blood glucose hourly for the first 3 hours. If stable between 4.0 and 10.0 mmol/L, 4hrly monitoring. Otherwise, 2hrly monitoring. If the serum glucose falls below 3.5 mmol/L, 30 min monitoring.		There was no association found between mean morning glucose levels and mortality. A 3.6-fold higher risk of mortality was linked to a single episode of hyperglycaemia. Even though the ideal glucose range is still unknown, maintaining serum glucose levels ≤10 mmol/L seems to strike a reasonable balance and may help prevent extremes in glucose values.
Pidcoke et al. (2007) **USA**	Investigations were conducted on patterns of blood glucose and exogenous insulin requirement in the intensive care unit.	156 patients		Readings via point of care monitors.	To create a 24-hour curve, the subjects' hourly blood glucose levels and insulin dosage requirements were matched for the time of day that the measurements were taken.		Insulin levels in healthy subjects are mirrored by the diurnal patterns of insulin requirement in critical injury, which may indicate the persistence of normal variability in insulin sensitivity. Midnight and noontime insulin requirement peaks and troughs, respectively, are probably inversely correlated with typical variations in insulin sensitivity, which peaks during the daytime when energy intake is high.

Table 2: Data extraction (continued)

Chase et al. (2010) **Belgium**	Virtual patients and in-silico virtual trial models and procedures are validated using matched cohorts from a tight glycaemic control clinical trial.	Group A: *n*=124 Group B: *n*=69	Group A: 4.4-6.1 mmol/L Group B: 7.8-10 mmol/L		Hourly blood glucose was recorded when the glycaemic level was not within the target range. 2-hourly measurements in the case of limited variation of glycaemia. 4-hourly when the glycaemic level was less than 50% of the highest glycemia of the four last hours.	A continuous intravenous infusion of insulin was given. Group A: Intensive insulin therapy. Group B: (p4) Conventional insulin therapy.	Overall, this study demonstrates the potential for models to provide accurate, safe, and efficient real-time TGC as well as the capability of model-based, data-driven in silico methods to support protocol design
Holm et al. (2004) **Ireland**	Blood glucose levels were evaluated in patients with severe burns receiving conventional management, and the relationship between early hyperglycaemia and clinical outcome was examined.	37 patients	10 - 11.1mmol/L	Measurement of blood glucose using arterial blood with a glucometer.	Blood glucose levels were taken 8, 16, 24, 36, and 48 hours following the thermal injury.	Maintaining glucose at a level between 10 and 11.1 mmol/L and administering insulin if the blood glucose level rose above 11.9 mmol/L.	Insulin resistance and hyperglycaemia are known to have detrimental effects. Prolonged and early hyperlgycaemia appear to be significant risk factors that may have an adverse effect on survival.
Kulkarni et al. (2005) **Australia**	Analysing the degree of agreement between two blood glucose measurement techniques used on patients in intensive	54 patients		Arterial blood using a blood gas analyser. Capillary blood using a glucometer.			We conclude that, for a general population of ICU patients, there is statistical agreement between arterial blood gas analysis and blood glucose measured from capillary blood using reagent strips

	care units: arterial blood using blood gas analyser with capillary blood using a reagent strip and glucometer						for patients who target a lower limit of blood glucose of 4.4 mmol/l. (p145) We advise using both strategies interchangeably but with caution.

RESULTS

After duplicates were removed, 1748 records were screened, 485 full text records and 1263 title/abstract records were assessed for eligibility; and 16 were included in the study (Fig 2). Another two records were included from the reference lists. The majority of studies included explored the sampling method of blood glucose (n=15, 83%). Thirteen studies (72%) looked at the target range of blood glucose, and ten studies explored the frequency of blood glucose testing (55%). Annexure (F) lists and summarises the studies included in the review.

Sampling method and measurements of blood glucose

The sampling of blood glucose was provided in 15 (83%) of the 18 articles mentioning sampling from arterial, central venous and capillary blood. Arterial blood was found to provide a more accurate blood glucose reading when using a glucometer according to Rodriguez-Delgado, García Del Moral, Cobos-Vargas, Martín-López and Colmenero (2022) as well as Ellis, Benjamin, Cornell, Decker, Farrell, McGugan et al. (2013). When starting insulin therapy caution should be taken if the blood glucose is solely based on capillary samples and when possible, results should be verified by Laboratory blood glucose readings to ascertain agreement (DuBose, Inaba, Branco, Barmparas, Lam, Teixeira et al., 2012).

Target range of blood glucose

The target blood glucose range were mentioned in 13 (72%) of the included studies. Strict glycaemic control or insulin therapy pursuing a target blood glucose control for critical ill patients of between 4.4.- 6.1 mmol/L was presented in six studies (Bleck, 2006; Chase, Pretty, Pfeifer, Shaw, Preiser, Le Compte et al., 2010; Graffagnino, Gurram, Kolls and Olson, 2010a; Green, O'Phelan, Bassin, Chang, Stern and Asai, 2010a; Kaukonen, Rantala, Pettilä and Hynninen, 2009; Mann, Jones, Wolf and

Wade, 2011) . Even tighter glucose control with insulin therapy targeting a blood glucose of 5 – 6.6 mmol/L to investigate the benefits of tight glycaemic control through intensive insulin therapy in critically ill patients were set (Gibson, Galiatsatos, Rabiee, Eaton, Abu-Hamdah, Christmas et al. (2009). In a study investigating the safety of intravenous insulin treatment in non-diabetic patients a strict glycaemic control target was set at 4.5 - 7 mmol/L (Staszewski, Brodacki, Kotowicz and Stepien, 2011). Another study using an insulin dose calculator attempted to improve glycaemic control by maintaining target values of between 5.4 - 7 mmol/L (Thomas, Marchant, Ogden and Collin, 2005).

Contrasting to tight blood glucose control some research suggest starting insulin administration when a patient's blood glucose was >12 mmol/L, after which the goal would be to maintain blood glucose between 10 - 11.1 mmol/L (Bleck, 2006). A conventional blood glucose range of 4.4 - 8.3 mmol/L was defined for the study done by Green et al. (2010a), whereby insulin therapy would be commenced if blood glucose is >8.3mmol/L. In a study done in a neuro-ICU, blood glucose levels were only treated with insulin if it exceeded 8.3 mmol/L (Graffagnino et al., 2010a; Mann et al., 2011). The set target for blood glucose levels ranged between 7.8-10 mmol/L, and insulin were started only when blood glucose levels were >10mmol/L in a study by Chase et al. (2010). Another study opted to maintain a blood glucose of <10mmol/L, and only intervene when blood glucose levels exceed 10mmol/L (Staszewski et al., 2011).

Frequency of blood glucose testing

The time frames for monitoring blood glucose levels were provided in 10 (55%) of the 18 articles. With strict glycaemic control, blood glucose was monitored hourly

until the target was reached followed by 2–4 hourly testing (Chase et al., 2010; Green et al., 2010a; Griesdale, Tremblay, McEwen and Chittock, 2009; Kaukonen et al., 2009; Mann et al., 2011; Staszewski et al., 2011).

The frequency of blood glucose testing was decreased when the reading was <50% than the previous reading (Chase et al., 2010). Six hourly blood glucose testing was done if the reading was <8.3 l/L (Green, O'Phelan, Bassin, Chang, Stern, Asai et al., 2010b). On the other end, blood glucose was done on admission and then only daily (Thomas et al., 2005). In burns patient population, blood glucose was tested only 8, 16, 24 and 36 hours following thermal injury (Holm, Hörbrand, Mayr, Henckel von Donnersmarck and Mühlbauer, 2004). Only one study reported that blood glucose was done every 30 minutes when patients presented with hypoglycaemia (Griesdale et al., 2009).

In a study by Pidcoke, Wade and Wolf (2007), daily insulin dosage requirements and hourly blood glucose levels were matched by subject for the time of day administered, and the glucose data were averaged to produce a 24-hour curve. They did not measure target values as such. Their objective was to investigate blood glucose patterns and exogenous insulin requirements in the intensive care unit.

DISCUSSION

The target ranges for blood glucose for critically ill patients provided are on average 4.4 – 10 mmol/L with the recommendation that insulin therapy to only be started when the blood glucose levels are between 8.3 – 12 mmol/L. Lower ranges of blood glucose levels have been associated with deceased mortality, neuropathy, and ventilation days (Bleck, 2006). However, no difference in the length of hospital stay was reported between the patients with lower or higher ranges of blood glucose which concluded that intensive insulin therapy was feasible and safe (Staszewski et

al., 2011). Patients on insulin therapy are prone to develop hypoglyceamia especially when lower ranges of blood glucose levels are targeted (Graffagnino et al., 2010a; Green et al., 2010b; Mann et al., 2011; Staszewski et al., 2011). Hypoglycaemic episodes were less likely to occur in patient groups targeting blood glucose values of ≤ 8.3mml/L or ≤ 10mmol/L, than in the stricter blood glucose control group (Graffagnino, Gurram, Kolls, Olson, Graffagnino, Gurram et al., 2010b; Griesdale et al., 2009).

In surgical patients managed with a higher blood glucose range sepsis has been reported of which 31% eventually passed away (Gibson et al., 2009). Any event of hyperglycemia, which include acceptance of blood glucose levels of up to 11.9 mmol/L, regardless of origin or effect, was linked to poor clinical result (Holm et al., 2004). Hyperglycaemia is an important indicator of poor short- and long-term outcomes for hospitalized patients, including increased mortality, length of hospital stay, and the requirement for continued care after discharge (Wu et al., 2022). Therefore, it is imperative that blood glucose monitoring and management is done frequently and accurately.

Existing practices in ICU use bedside glucometers to assess glucose levels every 30 to 60 minutes and change insulin titrations accordingly (Scrimgeour, Potz, Sellke and Abid, 2017). Regular insulin is administered intravenously and has a plasma half-life of less than 10 minutes. A single dose is typically cleared within 30 to 60 minutes. As a result, hypo- or hyperglycaemic episodes that may occur in between glucose tests may be missed by the glucose monitoring intervals (Scrimgeour et al., 2017).

Bedside blood glucose testing must be verified with laboratory results that can be timely and reportedly takes up to 45 minutes (Shearer, Boehmer, Closs, Dela Rosa,

Hamilton, Horton et al., 2009a). In addition, before taking a blood sample, the International Federation of Clinical Chemistry advises removing a volume three times larger than the "dead space" of the catheter and 5ml of blood should be discarded from the central line before analysis (Rodriguez-Delgado et al., 2022). In a study done by Shearer, Boehmer, Closs, Dela Rosa, Hamilton, Horton et al. (2009b) at least 7 ml of blood was removed from the central venous catheter for blood glucose testing. Other studies only stated that blood was drawn form a catheter, without explaining the method to sampling (DuBose et al., 2012; Ellis, Benjamin, Cornell, Decker, Farrell, McGugan et al., 2013; Kulkarni, Saxena, Price, O'Leary, Jacques and Myburgh, 2005; Petersen, Graves, Tacker, Okorodudu, Mohammad and Cardenas, 2008).

There is a set way of sampling capillary blood, according to the World health organization (WHO). In an adult patient, the finger is typically the preferred site for capillary testing. Because the pressure compresses the skin, a lancet that is somewhat shorter than the expected depth needed should be utilized. Order of sequence as follows: Apply alcohol to the entry site and allow to air dry. Puncture the skin with one quick, continuous, and deliberate stroke, to achieve a good flow of blood and to prevent the need to repeat the puncture. Wipe away the first drop of blood because it may be contaminated with tissue fluid or debris (sloughing skin). Avoid squeezing the finger or heel too tightly because this dilutes the specimen with tissue fluid (plasma) and increases the probability of haemolysis. When the blood collection procedure is complete, apply firm pressure to the site to stop the bleeding (WHO).

Furthermore, it is important to ensure that equipment used for blood glucose testing should be calibrated every 8 - 24 hours or as per hospital policy (Petersen et al., 2008). Only 50% of studies included in the review mentioned calibration methods.

STRENGTHS AND LIMITATIONS

The review included articles published anywhere between 2001 to 2023, although it is possible that not all the literature on the management of dysglycaemia was identified. The review provides and overview of the existing literature identifying shortcomings and ideas for further research. Although many studies on blood glucose testing and insulin therapy have been conducted it focuses on diabetic patients, where therefore hope that this would create awareness about dysglycaemia among critically ill patients without diabetes. Data extraction and interpretation of results was difficult at times, as articles did not specifically mention at what stage in critical illness blood glucose was tested so the results may reflect inaccurately.

SUGGESTIONS FOR FUTURE RESEARCH

Diabetic and non-diabetic patients are not distinguished in studies assessing glycaemic control targets and protocols in critically ill patients (Sreedharan et al., 2022). Further research can be aimed at distinguishing between diabetic and non-diabetic and the effect and treatment of dysglycaemia. Additionally, research suggesting intensive insulin therapy for patients in intensive care units has yielded conflicting results, suggesting that patients without diabetes benefit from the therapy while those with diabetes does not (Lee et al., 2020).

In order to reach conclusions, more research on the same variables should be done (homogenic studies). Additional research is required to evaluate target range values, sampling frequency, and the most practical approach for the best possible

patient outcomes. Limited studies have been conducted in a South-African context, so future research may focus on studies within South-African healthcare settings on the management of dysglycaemia.

CONCLUSION

Management of dysglycaemia still happens ad hoc, and outcomes differ vastly. Critically ill patients cared for in ICU needs a focused pathway for dysglycaemia to improve patient outcomes. Much more research is required to investigate the frequency, method of blood glucose testing when critically ill patients are managed with insulin therapy. It is time for critical care nurses to critically reflect on interpretation and management of the fifth vital sign.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

ACKNOWLEDGEMENT

I would like to thank Ms. N. Puzicha for editing this manuscript.

Chapter 5: Limitations and recommendations for future research

5.1 Introduction

The scoping review was done to investigate and review the available management strategies of dysglycaemia. Many discrepancies have been found regarding the sampling of blood glucose, frequency of testing, target range as well as outcomes regarding these interventions. More research is needed in order to establish which target range, sampling method and time frame of drawing blood glucose is best for optimal outcomes.

5.2 Suggestions for future research

Studies evaluating glycaemic control targets and protocols in critically ill patients do not distinguish between diabetic and non-diabetic patients (Sreedharan et al., 2022). Further research can be aimed at distinguishing between diabetic and non-diabetic and the effect and treatment of dysglycaemia. Furthermore, studies recommending intensive insulin therapy for ICU patients have produced inconsistent findings whereby patients without diabetes benefit from the therapy while those with diabetes do not (Lee et al., 2020).

More studies should be conducted, to focus on comparing the same variables to draw conclusions (homogenic studies). Further studies need to be conducted in order to test target range values as well as frequency of sampling and also which method is most feasible for optimal patient outcomes.

Limited studies have been conducted in a South-African context, so future research may focus on studies within South-African healthcare settings on the management of dysglycaemia.

5.3 Strengths of this study

This review may be of benefit in the South-African health system where the researcher is employed, to raise awareness in the management of dysglycaemia. It may highlight some of the issues and shortcomings in the management of dysglycaemia and may assist nurses in the management thereof.

5.4 Limitations of this study

Many studies have been excluded during the screening process, especially those including the diabetic population. This may not be a true reflection of results of this study. This review specifically looked at the non-diabetic population. Data extraction and interpretation of results was difficult at times, as articles did not specifically mention at what stage in critical illness blood glucose was tested (as seen from pathophysiology- glucose fluctuates during different stages of ICU stay), so the results may reflect inaccurately(Staszewski et al., 2011).

5.5 Conclusion

This review highlighted the different management strategies of dysglycaemia in the critical care unit. The available literature shows that there is lacking evidence of standardised care regarding the critically ill patient population. There is still no consensus regarding optimal target range of blood glucose, as well as frequency of blood glucose measured as studies had different outcomes in their study groups. Our review highlights the need for further research to refine values and standards of care.

References

Abu-Samah, A., Knopp, J.L., Abdul Razak, N.N., Razak, A.A., Jamaludin, U.K., Mohamad Suhaimi, F., Md Ralib, A., Mat Nor, M.B., Chase, J.G. and Pretty, C.G., 2019. Model-based glycemic control in a Malaysian intensive care unit: performance and safety study. Medical Devices: Evidence and Research, pp.215-226.

Al-Yousif, N., Rawal, S., Jurczak, M., Mahmud, H., Shah, F.A. 2021. Endogenous glucose production in critical illness. Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition. 36(2):344-59.

Alotair, H.A., Aldasoqi, S.A., Baldove, J.P. and Abdou, M.A., 2019. Glycemic control in intensive care unit: Experience of a tertiary care center. Journal of Nature and Science of Medicine, 2(4), pp.215-219.

Aramendi, I., Burghi, G., Manzanares, W. 2017. Dysglycemia in the critically ill patient: Current evidence and future perspectives. Revista Brasileira de terapia intensiva. 29(3):364-372.

Arksey, H., O'malley, L. 2005. Scoping studies: Towards a methodological framework. International journal of social research methodology. 8(1):19-32.

Bagshaw, S.M., Bellomo, R., Jacka, M.J., Egi, M., Hart, G.K., George, C. 2009. The impact of early hypoglycemia and blood glucose variability on outcome in critical illness. Critical Care. 13(3):1-10.

Balintescu, A., Palmgren, I., Lipcsey, M., Oldner, A., Larsson, A., Cronhjort, M., et al. 2021. Prevalence and impact of chronic dysglycemia in intensive care unit patients-a retrospective cohort study. Acta Anaesthesiologica Scandinavica. 65(1):82-91.

Bleck, T.P., 2006. Intensive insulin therapy reduced the incidence of neurologic complications in critically ill patients. ACP J Club, 144, p.20.

Bochicchio, G.V., Nasraway, S.A., Moore, L.J., Furnary, A.P., Nohra, E.A., Bochicchio, K.M., et al. 2021. Fifteen-minute frequency of glucose measurements and the use of threshold alarms: Impact on mitigating dysglycemia in critically ill patients. Journal of Diabetes Science and Technology. 15(2):279-86.

Brunkhorst, F.M., Engel, C., Bloos, F., Meier-Hellmann, A., Ragaller, M., Weiler, N., Moerer, O., Gruendling, M., Oppert, M., Grond, S. and Olthoff, D., 2008. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. New England Journal of Medicine, 358(2), pp.125-139.

Canseco, J.A., Chang, M., Karamian, B.A., Nicholson, K., Patel, P.D., Shenoy, K., Hartman, J., Kurd, M.F., Rihn, J.A., Anderson, D.G. and Hilibrand, A.S., 2022. Postoperative glycemic variability as a predictor of adverse outcomes following lumbar fusion. Spine, 47(7), pp.E304-E311.

Chase, J.G., Pretty, C.G., Pfeifer, L., Shaw, G.M., Preiser, J.C., Le Compte, A.J., Lin, J., Hewett, D., Moorhead, K.T. and Desaive, T., 2010. Organ failure and tight glycemic control in the SPRINT study. Critical care, 14, pp.1-13.

Chase, J.G., Desaive, T., Bohe, J., Cnop, M., De Block, C., Gunst, J., Hovorka, R., Kalfon, P., Krinsley, J., Renard, E. and Preiser, J.C., 2018. Improving glycemic control in critically ill patients: personalized care to mimic the endocrine pancreas. Critical Care, 22, pp.1-10.

Chen, X., Bi, J., Zhang, J., Du, Z., Ren, Y., Wei, S., Ren, F., Wu, Z., Lv, Y. and Wu, R., 2019. The impact of serum glucose on the predictive value of serum lactate for hospital mortality in critically Ill surgical patients. Disease Markers, 2019.

Deane, A.M., Plummer, M.P. and Ali Abdelhamid, Y., 2022. Update on glucose control during and after critical illness. Current Opinion in Critical Care, 28(4), pp.389-394.

Deng, T., Liu, M., Pan, L., Jiang, K. and Li, Y., 2021. A comparison of arterial blood glucose and peripheral blood glucose levels in critically ill patients: measurements

using the arterial blood gas analyzer and the rapid glucose meter. Ann Palliat Med, 10(3), pp.3179-3184.

DuBose, J.J., Inaba, K., Branco, B.C., Barmparas, G., Lam, L., Teixeira, P.G., Belzberg, H. and Demetriades, D., 2012. Discrepancies between capillary glucose measurements and traditional laboratory assessments in both shock and non-shock states after trauma. journal of surgical research, 178(2), pp.820-826.

Eerdekens, G.J., Rex, S. and Mesotten, D., 2020. Accuracy of blood glucose measurement and blood glucose targets. Journal of Diabetes Science and Technology, 14(3), pp.553-559.

Ellis, M.F., Benjamin, K., Cornell, M., Decker, K., Farrell, D., McGugan, L., Porter, G.P., Shearin, H., Zhao, Y. and Granger, B.B., 2013. Suitability of capillary blood glucose analysis in patients receiving vasopressors. American Journal of Critical Care, 22(5), pp.423-429.

Enang, O.E., Otu, A.A., Essien, O.E., Okpara, H., Fasanmade, O.A., Ohwovoriole, A.E. and Searle, J., 2014. Prevalence of dysglycemia in Calabar: a cross-sectional observational study among residents of Calabar, Nigeria. BMJ open diabetes research & care, 2(1).

Englert, R.M. and Yablonsky, A.M., 2019. Scoping review and gap analysis of research related to the health of women in the US military, 2000 to 2015. Journal of Obstetric, Gynecologic & Neonatal Nursing, 48(1), pp.5-15.

Fortmann, A.L., Spierling Bagsic, S.R., Talavera, L., Garcia, I.M., Sandoval, H., Hottinger, A. and Philis-Tsimikas, A., 2020. Glucose as the fifth vital sign: a randomized controlled trial of continuous glucose monitoring in a non-ICU hospital setting. Diabetes Care, 43(11), pp.2873-2877.

Fowler, R.A., Lapinsky, S.E., Hallett, D., Detsky, A.S., Sibbald, W.J., Slutsky, A.S. and Stewart, T.E., 2003. Critically ill patients with severe acute respiratory syndrome. Jama, 290(3), pp.367-373.

Fujishima, S., Gando, S., Saitoh, D., Kushimoto, S., Ogura, H., Abe, T., Shiraishi, A., Mayumi, T., Sasaki, J., Kotani, J. and Takeyama, N., 2021. Incidence and impact of dysglycemia in patients with sepsis under moderate glycemic control. Shock, 56(4), pp.507-513.

Gibson, B.R., Galiatsatos, P., Rabiee, A., Eaton, L., Abu-Hamdah, R., Christmas, C., Milner, S.M., Andersen, D.K. and Elahi, D., 2009. Intensive insulin therapy confers a similar survival benefit in the burn intensive care unit to the surgical intensive care unit. Surgery, 146(5), pp.922-930.

Godwin L, Tariq MA, Crane JS. 2019. Histology, Capillary. In: StatPearls. StatPearls Publishing, Treasure Island (FL); 2023. PMID: 31536187.

Graffagnino, C., Gurram, A.R., Kolls, B. and Olson, D.M., 2010. Intensive insulin therapy in the neurocritical care setting is associated with poor clinical outcomes. Neurocritical care, 13, pp.307-312.

Green, D.M., O'Phelan, K.H., Bassin, S.L., Chang, C.W., Stern, T.S. and Asai, S.M., 2010. Intensive versus conventional insulin therapy in critically ill neurologic patients. Neurocritical care, 13, pp.299-306.

Griesdale, D.E., Tremblay, M.H., McEwen, J. and Chittock, D.R., 2009. Glucose control and mortality in patients with severe traumatic brain injury. Neurocritical care, 11, pp.311-316.

Hantzidiamantis, P.J. and Lappin, S.L., 2022. Physiology, Glucose. StatPearls. Treasure Island (FL).

Holm, C., Hörbrand, F., Mayr, M., von Donnersmarck, G.H. and Mühlbauer, W., 2004. Acute hyperglycaemia following thermal injury: friend or foe?. Resuscitation, 60(1), pp.71-77.

Investigators, N.-S.S. 2009. Intensive versus conventional glucose control in critically ill patients. New England Journal of Medicine. 360(13):1283-97.

Joshi, A. and Mehta, Y., 2022. Dysglycemia in ICU Patients. Journal of Cardiac Critical Care TSS, 6(01), pp.040-042.

Kaukonen, K.M., Rantala, M., Pettilä, V. and Hynninen, M., 2009. Severe hypoglycemia during intensive insulin therapy. Acta anaesthesiologica scandinavica, 53(1), pp.61-65.

Kesavadev, J., Misra, A., Saboo, B., Aravind, S.R., Hussain, A., Czupryniak, L. and Raz, I., 2021. Blood glucose levels should be considered as a new vital sign indicative of prognosis during hospitalization. Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 15(1), pp.221-227.

Khalil, H., Peters, M.D., Tricco, A.C., Pollock, D., Alexander, L., McInerney, P., Godfrey, C.M. and Munn, Z., 2021. Conducting high quality scoping reviews-challenges and solutions. Journal of clinical epidemiology, 130, pp.156-160.

Kim, T.J., Lee, J.S., Park, S.H. and Ko, S.B., 2021. Short-term glycemic variability and hemorrhagic transformation after successful endovascular thrombectomy. Translational Stroke Research, pp.1-8.

Klonoff, D.C., Wang, J., Rodbard, D., Kohn, M.A., Li, C., Liepmann, D., Kerr, D., Ahn, D., Peters, A.L., Umpierrez, G.E. and Seley, J.J., 2023. A glycemia risk index (GRI) of hypoglycemia and hyperglycemia for continuous glucose monitoring validated by clinician ratings. Journal of diabetes science and technology, 17(5), pp.1226-1242.

Korpi-Steiner, N., Horowitz, G., Tesfazghi, M. and Suh-Lailam, B.B., 2023. Current Issues in Blood Gas Analysis. The Journal of Applied Laboratory Medicine, 8(2), pp.372-381.

Krinsley, J.S., 2004, August. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. In Mayo Clinic Proceedings (Vol. 79, No. 8, pp. 992-1000). Elsevier.

Krinsley, J.S., 2004. Intensive glucose control in the ICU: An expert interview with James S. Krinsley, MD by Antonios Liolios. MedGenMed: Medscape general medicine, 6(2), p.33.

Krinsley, J.S. and Preiser, J.C., 2019. Is it time to abandon glucose control in critically ill adult patients?. Current Opinion in Critical Care, 25(4), pp.299-306.

Kulkarni, A., Saxena, M., Price, G., O'Leary, M.J., Jacques, T. and Myburgh, J.A., 2005. Analysis of blood glucose measurements using capillary and arterial blood samples in intensive care patients. Intensive care medicine, 31, pp.142-145.

Kushimoto, S., Abe, T., Ogura, H., Shiraishi, A., Saitoh, D., Fujishima, S., Mayumi, T., Hifumi, T., Shiino, Y., Nakada, T.A. and Tarui, T., 2020. Impact of blood glucose abnormalities on outcomes and disease severity in patients with severe sepsis: an analysis from a multicenter, prospective survey of severe sepsis. PLoS One, 15(3), pp.1-15.

Lee, T.F., Drake, S.M., Roberts, G.W., Bersten, A., Stranks, S.N., Heilbronn, L.K., Mangoni, A.A. and Burt, M.G., 2020. Relative hyperglycemia is an independent determinant of in-hospital mortality in patients with critical illness. Critical care medicine, 48(2), pp.e115-e122.

Leszek, S. 2017. Glucose homeostasis. In: Weizhen, Z. (eds.) Gluconeogenesis. Rijeka: IntechOpen.

Levac, D., Colquhoun, H. and O'Brien, K.K., 2010. Scoping studies: advancing the methodology. Implementation science, 5, pp.1-9.

Levitt, N.S., Peer, N., Steyn, K., Lombard, C., Maartens, G., Lambert, E.V. and Dave, J.A., 2016. Increased risk of dysglycaemia in South Africans with HIV; especially those on protease inhibitors. Diabetes research and clinical practice, 119, pp.41-47.

Li, J., Jia, L., Ma, W., Feng, Y., Yu, H. and Du, H., 2022. Dietary iron modulates hepatic glucose homeostasis via regulating gluconeogenesis. The Journal of Nutritional Biochemistry, 109, pp.1-9.

Lockwood, C. and Tricco, A.C., 2020. Preparing scoping reviews for publication using methodological guides and reporting standards. Nursing & Health Sciences, 22(1), pp.1-4.

Long, M.T. and Coursin, D.B., 2020. The perils of perioperative dysglycemia. International Anesthesiology Clinics, 58(1), pp.21-26.

Lu, Z., Tao, G., Sun, X., Zhang, Y., Jiang, M., Liu, Y., Ling, M., Zhang, J., Xiao, W., Hua, T. and Zhu, H., 2022. Association of blood glucose level and glycemic variability with mortality in sepsis patients during ICU hospitalization. Frontiers in Public Health, 10, pp. 1-14.

MacDonald, A.J., Yang, Y.H.C., Cruz, A.M., Beall, C. and Ellacott, K.L., 2021. Brain-body control of glucose homeostasis—Insights from model organisms. Frontiers in Endocrinology, 12, p.662769.

Mann, E.A., Jones, J.A., Wolf, S.E. and Wade, C.E., 2011. Computer decision support software safely improves glycemic control in the burn intensive care unit: a randomized controlled clinical study. Journal of burn care & research, 32(2), pp.246-255.

Marshall, J.C., Bosco, L., Adhikari, N.K., Connolly, B., Diaz, J.V., Dorman, T., Fowler, R.A., Meyfroidt, G., Nakagawa, S., Pelosi, P. and Vincent, J.L., 2017. What is an intensive care unit? A report of the task force of the World Federation of Societies of Intensive and Critical Care Medicine. Journal of critical care, 37, pp.270-276.

McGowan, J., Straus, S., Moher, D., Langlois, E.V., O'Brien, K.K., Horsley, T., Aldcroft, A., Zarin, W., Garitty, C.M., Hempel, S. and Lillie, E., 2020. Reporting scoping reviews—PRISMA ScR extension. Journal of clinical epidemiology, 123, pp.177-179.

Mcmillan, J.M. 1990. Blood glucose. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition.

Mitsuyama, Y., Shimizu, K., Komukai, S., Hirayama, A., Takegawa, R., Ebihara, T., Kitamura, T., Ogura, H. and Shimazu, T., 2022. Sepsis-associated hypoglycemia on admission is associated with increased mortality in intensive care unit patients. Acute Medicine & Surgery, 9(1), pp. 1-8.

Mörgeli, R., Wollersheim, T., Engelhardt, L.J., Grunow, J.J., Lachmann, G., Carbon, N.M., Koch, S., Spies, C. and Weber-Carstens, S., 2021. Critical illness myopathy precedes hyperglycaemia and high glucose variability. Journal of Critical Care, 63, pp.32-39.

Munn, Z., Pollock, D., Khalil, H., Alexander, L., Mclnerney, P., Godfrey, C.M., Peters, M. and Tricco, A.C., 2022. What are scoping reviews? Providing a formal definition of scoping reviews as a type of evidence synthesis. JBI Evidence Synthesis, 20(4), pp.950-952.

Nakiriba, R., Mayega, R.W., Piloya, T., Nabukeera-Barungi, N. and Idro, R., 2018. Prevalence and factors associated with dysglycemia among girls in selected boarding secondary schools in Wakiso District, Uganda. Adolescent Health, Medicine and Therapeutics, pp.167-176.

Network, E. 2019. Reporting guidelines. URL: https://www. equator-network. org/reporting-guidelines/[accessed 2021-08-24].

Njuguna, B., Kiplagat, J., Bloomfield, G.S., Pastakia, S.D., Vedanthan, R. and Koethe, J.R., 2018. Prevalence, risk factors, and pathophysiology of dysglycemia among people living with HIV in Sub-Saharan Africa. Journal of diabetes research, 2018.

Ohbe, H., Matsui, H. and Yasunaga, H., 2021. Intensive care unit versus high-dependency care unit for patients with acute heart failure: a nationwide propensity score-matched cohort study. Journal of Intensive Care, 9, pp.1-10.

Peters, M.D., Marnie, C., Tricco, A.C., Pollock, D., Munn, Z., Alexander, L., McInerney, P., Godfrey, C.M. and Khalil, H., 2020. Updated methodological guidance for the conduct of scoping reviews. JBI evidence synthesis, 18(10), pp.2119-2126.

Peters, M.D., Godfrey, C., McInerney, P., Khalil, H., Larsen, P., Marnie, C., Pollock, D., Tricco, A.C. and Munn, Z., 2022. Best practice guidance and reporting items for the development of scoping review protocols. JBI evidence synthesis, 20(4), pp.953-968.

Petersen, J.R., Graves, D.F., Tacker, D.H., Okorodudu, A.O., Mohammad, A.A. and Cardenas Jr, V.J., 2008. Comparison of POCT and central laboratory blood glucose results using arterial, capillary, and venous samples from MICU patients on a tight glycemic protocol. Clinica Chimica Acta, 396(1-2), pp.10-13.

Pidcoke, H.F., Wade, C.E. and Wolf, S.E., 2007. Insulin and the burned patient. Critical care medicine, 35(9), pp.S524-S530.

Plummer, M.P., Hermanides, J. and Deane, A.M., 2022. Is it time to personalise glucose targets during critical illness?. Current Opinion in Clinical Nutrition and Metabolic Care, 25(5), pp.364-369.

Pollock, D., Davies, E.L., Peters, M.D., Tricco, A.C., Alexander, L., McInerney, P., Godfrey, C.M., Khalil, H. and Munn, Z., 2021. Undertaking a scoping review: A practical guide for nursing and midwifery students, clinicians, researchers, and academics. Journal of advanced nursing, 77(4), pp.2102-2113.

Röder, P.V., Wu, B., Liu, Y. and Han, W., 2016. Pancreatic regulation of glucose homeostasis. Experimental & molecular medicine, 48(3), pp.e219-e219.

Rodriguez-Delgado, E., Garcia del Moral, R., Cobos-Vargas, A., Martín-López, J. and Colmenero, M., 2022. Agreement of blood glucose measured with glucose meter in arterial, central venous, and capillary samples in adult critically ill patients. Nursing in Critical Care, 27(5), pp.711-717.

Salinas, P.D. and Mendez, C.E., 2019. Glucose management technologies for the critically ill. Journal of diabetes science and technology, 13(4), pp.682-690.

Sanaie, S. and Mahmoodpoor, A., 2017. Dysglycemia in Critically Ill Patients: Common Problems and Future Direction. Advances in Bioscience and Clinical Medicine, 5(3), pp.1-2.

Scrimgeour, L.A., Potz, B.A., Sellke, F.W. and Abid, M.R., 2017. Continuous glucose monitoring in the cardiac ICU: current use and future directions. Clinical medicine research, 6(6), p.173.

See, K.C., 2021. Glycemic targets in critically ill adults: a mini-review. World Journal of Diabetes, 12(10), p.1719.

Shearer, A., Boehmer, M., Closs, M., Dela Rosa, R., Hamilton, J., Horton, K., McGrath, R. and Schulman, C., 2009. Comparison of glucose point-of-care values with laboratory values in critically ill patients. American Journal of Critical Care, 18(3), pp.224-230.

Sreedharan, R., Martini, A., Das, G., Aftab, N., Khanna, S. and Ruetzler, K., 2022. Clinical challenges of glycemic control in the intensive care unit: A narrative review. World Journal of Clinical Cases, 10(31), p.11260.

Staszewski, J., Brodacki, B., Kotowicz, J. and Stepien, A., 2011. Intravenous insulin therapy in the maintenance of strict glycemic control in nondiabetic acute stroke patients with mild hyperglycemia. Journal of stroke and cerebrovascular diseases, 20(2), pp.150-154.

Sucharew, H. and Macaluso, M., 2019. Methods for research evidence synthesis: The scoping review approach. Journal of hospital medicine, 14(7), pp.416-418.

Switzer, E., Schellenberg, M., Lewis, M., Owattanapanich, N., Lam, L. and Inaba, K., 2021. Hypoglycemia in a Surgical Intensive Care Unit. The American Surgeon, 87(10), pp.1580-1583.

Thomas, A.N., Marchant, A.E., Ogden, M.C. and Collin, S., 2005. Implementation of a tight glycaemic control protocol using a web-based insulin dose calculator. Anaesthesia, 60(11), pp.1093-1100.

Tickoo, M. 2019. The long and winding road to personalized glycemic control in the intensive care unit. Seminars in Respiratory and Critical Care Medicine. 40(05):571-579.

Tricco, A.C., Lillie, E., Zarin, W., O'brien, K., Colquhoun, H., Kastner, M., Levac, D., Ng, C., Sharpe, J.P., Wilson, K. and Kenny, M., 2016. A scoping review on the conduct and reporting of scoping reviews. BMC medical research methodology, 16, pp.1-10.

Tricco, A.C., Lillie, E., Zarin, W., O'Brien, K.K., Colquhoun, H., Levac, D., Moher, D., Peters, M.D., Horsley, T., Weeks, L. and Hempel, S., 2018. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Annals of internal medicine, 169(7), pp.467-473.

Uyttendaele, V., Dickson, J.L., Shaw, G.M., Desaive, T. and Chase, J.G., 2017. Untangling glycaemia and mortality in critical care. Critical Care, 21, pp.1-17.

Van den Berghe, G., Wilmer, A., Hermans, G., Meersseman, W., Wouters, P.J., Milants, I., Van Wijngaerden, E., Bobbaers, H. and Bouillon, R., 2006. Intensive insulin therapy in the medical ICU. New England journal of medicine, 354(5), pp.449-461.

Van den Berghe, G., Wouters, P., Weekers, F., Verwaest, C., Bruyninckx, F., Schetz, M., Vlasselaers, D., Ferdinande, P., Lauwers, P. and Bouillon, R., 2001. Intensive insulin therapy in critically ill patients. New England journal of medicine, 345(19), pp.1359-1367.

Van Steen, S.C., Rijkenberg, S., Limpens, J., Van der Voort, P.H., Hermanides, J. and DeVries, J.H., 2017. The clinical benefits and accuracy of continuous glucose monitoring systems in critically ill patients—a systematic scoping review. Sensors, 17(1), p.146.

Weiner, C.P. and Buhimschi, C. 2009. I. In: Weiner, C.P.Buhimschi, C. (eds.) Drugs for pregnant and lactating women (second edition). Philadelphia: W.B. Saunders.

Wilcox, G., 2005. Insulin and insulin resistance. Clinical biochemist reviews, 26(2), p.19-39.

Wong S, Tran MD, Tsu L. Hyperglycemia and insulin management in critically ill patients. US Pharm. 2021 ; 46 (11): HS7-HS12. https://www.uspharmacist.com/article/hyperglycemia-and-insulin-management-in-critically-ill-patients/

Wu, Z., Liu, J., Zhang, D., Kang, K., Zuo, X., Xu, Q., Pan, A., Fang, W., Liu, F., Shang, Y. and Yin, H., 2022. Expert consensus on the glycemic management of critically ill patients. Journal of Intensive Medicine, 2(03), pp.131-145.

Yamada, T., Shojima, N., Hara, K., Noma, H., Yamauchi, T. and Kadowaki, T., 2017. Glycemic control, mortality, secondary infection, and hypoglycemia in critically ill pediatric patients: a systematic review and network meta-analysis of randomized controlled trials. Intensive Care Medicine, 43(9), pp.1-15.

ANNEXURE A: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	Page iv, v
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	Page 3, 4, 21, 22,
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	Page iv, v, 25, 26
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration	NA

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
		information, including the registration number.	
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	Page iv, 37
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	Page iv, v, 35
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Page 35, Annexure Ci,Cii
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	Page 35, 36, 45, Annexure D
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	Page 37

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	Page 37
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	NA
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	Page 45
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	Page 35, Annexure D
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Annexure F
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	NA
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Annexure F,38
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	Page v, 45

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	Page 50, 53
Limitations	20	Discuss the limitations of the scoping review process.	Page 50, 53
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	Page 50
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	No funding obtained for this study

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.
* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.
† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).
‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.
§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

ANNEXURE B – DATA EXTRACTION TABLE

Author/s & country of publication	Objective of study	Population	Target range of blood glucose	Sampling method of blood glucose	Frequency of blood glucose testing	Method of insulin or dextrose administration (i.e., protocol type etc)	Outcomes/ Results
Rodriguez et al. (2022) **Spain**	Analysis of the agreement between arterial, central venous, and capillary blood samples using glucose meter in critically ill patients	A total of 297 measurements from 54 patients were included in the study.		Central venous catheter blood, arterial blood and capillary blood samples were taken.		Subcutaneous insulin was used to treat the majority of patients, accounting for 93% (276) of the measures.	When a glucose meter is used, there is little agreement between arterial, capillary, and central venous samples for blood glucose readings.
Bleck (2006) **Belgium**	To ascertain whether intensive insulin therapy improve neurologic outcomes in critically ill patients.	1548 critically ill ventilated patients.	Intensive insulin therapy group: strict glycaemic control: 4.4and 6.1 mmol/L. Usual care group: commence insulin therapy if blood glucose > 12 mmol/L, maintain blood glucose at 10.0 -11.1mmol/L.				Intensive insulin therapy decreased the likelihood of additional prolonged ventilation and neurologic complications in critically ill patients with isolated brain injury or prolonged ventilation.
Ellis et al. (2013) **Durham**	To compare arterial blood samples using the clinical chemistry lab with capillary and	50 adult post-operative cardiothoracic patients		Capillary and arterial sites. Clinical chemistry laboratory testing (CLT)			Findings demonstrated that the capillary point of care testing produced low and unacceptable agreement levels

	arterial blood samples using pint of care testing in patients following cardiothoracic surgery			and point of care testing (POCT) were used to test the samples.			with the gold standard clinical chemistry lab. Since arterial point of care testing and the clinical chemistry lab's results agreed within a 95% acceptable range, arterial point of care testing is safe for the use of insulin infusions.
Green et al. (2010) **Hawaii**	To ascertain whether maintaining blood glucose levels between 4.4 and 6.1 mmol/L with intensive insulin therapy (IIT) or below 8.3 mmol/L with conventional treatment was linked to a lower rate of mortality and better functional outcomes in critically ill patients.	81 patients	Intensive control group (range of 4.4-6.1mmol/L) *n*=45 Conventional control group (range <8.3mmol/L) (range 4.4-8.3mmol/L) *n*=36	Intensive group: Arterial catheter, or capillary blood (fingerstick). Conventional group: Arterial line or capillary blood (fingerstick). A glucometer was primarily used to measure the level of glucose.	Intensive group: Initially 1hrly, then 2hrly until levels stabilised. Conventional group: Every 6 hrs.	Intensive group: continuous insulin infusion titrated to achieve a target blood sugar level of 4.4–6.1 mmol/L. Conventional group: Start treatment if blood glucose > 8.3 mmol/L. Subcutaneous insulin (sliding scale) for a blood sugar of 8.3-11.1mmol/L.	IIT showed no benefit in this small group of critically ill neurologic patients, as there was no significant difference in mortality, morbidity, ICU length of stay, or functional outcome.
Mann et al. (2011) **Texas**	To ascertain whether serum glucose concentration control in a burn intensive care unit can be achieved safely and effectively with the use of computer decision support software (CDSS).	Standard of care paper protocol (PP) Computer protocol (CP) CP group: *n*=10 PP group: *n*=8	For both standard of care paper protocol (PP) or Computer protocol (CP): 4.4 - 6.1mmol/L:	Point-of-care glucometers was used.	PP group: 2 hrly CP group max. 1 hrly	Insulin therapy were started if two hourly serum glucose measurements were≥ 8.3mmol/L, then hourly blood glucose measurements guided the insulin titration Dextrose were given at	Compared to a conservative paper-based nomogram, CDSS enabled burn ICU patients to achieve target glucose more frequently, improving glycaemic control. There was also no discernible increase in the risk of hypoglycaemic events.

						values less than 3.8mmol/L	
Gibson et al. (2009) **Baltimore**	To ascertain whether strict glyceamic control achieved by intensive insulin therapy (IIT) is beneficial for critically ill burn patients.	37 patients Surgical ICU - *n=22* Burns ICU - *n=15*	- Tight glycaemic control: average <8.3mmol/L - Poor glycaemic control: average >8.3mmol/L	The measurements of blood glucose obtained from finger sticks, from laboratory values obtained from scheduled venous samples, and/or from arterial blood samples taken from an indwelling catheter.	Until three consecutive glucose readings fall within the desired glucose range of 5-6.6 mmol/L without necessitating an adjustment to the insulin infusion, glucose measurement ta ken at least once every hour.	Yale insulin infusion protocol	Patients on IIT who have strict glyceamic control have lower mortality rates in the Burns ICU (20% vs.50%) and Surgical ICU (0% vs. 58%). In the Burns ICU, patient survival has been associated with strict glycaemic control, as well as a lower rate of total body surface area burn.
Shearer et al. (2009) **Portland**	To compare the glucose measurements obtained from a point-of-care (POC) device for catheter and fingerstick blood samples with those obtained from clinical laboratory analysis of a catheter blood sample.	The study included 63 critically ill adult patients.		Central venous catheter blood: - for central lab analysis - for POC device Fingerstick (capillary blood) - for POC device			Significant statistical and clinical differences were observed between laboratory and point-of-care glucose readings. Point of care values for fingerstick (capillary) and CVC blood samples did not differ. It is acceptable in critical care units to use both capillary and CVC blood interchangeably when performing point of care testing.

Graffagnino et al. (2010). **USA**	A program of IIT (intensive insulin therapy) to achieve a blood glucose of 4.4-6.6 mmol/L. (p307).	3,709 patients	Standard insulin therapy: Blood glucose level: 8.3mmol/L Intensive insulin therapy: Insulin therapy was titrated to achieve glucose levels between 4.4-6.6mmol/L Moderate hypoglycaemia: <3.8 mmol/L, severe hypoglycaemia as <2.2 mmol/L, extreme hypoglycaemia as <1.1 mmol/L Hyperglycaemia: - Blood glucose level > 16.6mmol/L - severe - Blood glucose level of 6.1-8.0 mmol/L - mild	Capillary blood obtained using a blood glucose monitor via venous or fingerstick sampling.		To maintain the lower glucose set points, adjustments were made to both the continuous insulin drip protocol and the modified multi-dosing insulin protocol.	An increased risk of mortality was linked to hyperglycaemia (> 16.6 mmol/L) in a group of patients suffering from critical illnesses. When glycaemic control was achieved through an intensive insulin strategy (target glucose level 4.4–6.6 mmol/L), the probability of hypoglycaemic episodes increased in comparison to the more conservative standard approach (target glucose <8.3 mmol/L). Any level of hypoglycaemia was linked to a higher death rate.

Staszewski et al. (2011) **Poland**	To determine whether intravenous (IV) insulin treatment is safe and effective in reducing mortality and functional short-term disability in nondiabetic AIS patients with mild hyperlgycaemia by achieving strict glycaemic control.	ISI: intravenous insulin infusion- *n*=26 CG: control group - *n*=24	ISI group: - Blood glucose range: 4.5 – 7 mmol/L. *strict glycaemic control.* CG: - Blood glucose <10mmol/L *(commence treatment if >10mmol/L)*	ISI group: - Capillary blood CG: - Capillary blood	ISI group: - Initially 1hrly until within the targeted range, then decreased to every 4 hrly. CG: - 4hrly	ISI group: - 24-hour IV insulin infusion CG: - Subcutaneous insulin Symptomatic hypoglycaemia was treated with dextrose and blood glucose was rechecked every 15 minutes. If hypoglycaemia persists, protocol treatment was continued.	Intensive 24-hour intravenous insulin therapy is a relatively safe and effective treatment option for non-diabetic patients with mild post-stroke hyperglycaemia. Maintaining blood glucose at 7 mmol/L for the first 24 hours following ictus may lessen neurologic impairment.
Petersen et al. (2008) **USA**	The difference between a point-of-care glucose meter and the main clinical laboratory for medical intensive care unit patients on a strict glycaemic protocol were investigated. Investigated whether the location of blood sampling had a significant impact on glucose values.	84 patients.	Hypoglycaemia: venous plasma glucose <3.9 mmol/L. Clinically significant hypoglycaemia: <2.2 mmol/L.	- Arterial blood - Central venous catheter blood. - Capillary blood (fingerstick). - Point of care meter was used for all 3 sources - Arterial and venous blood - blood gas analyser - Arterial and venous blood collected in blood tubes and sent to main clinical laboratory for		For hypoglycaemia: Blood glucose measurements were taken every 15 to 30 minutes until the blood glucose reached at least 5.0 mmol/L, and then hourly after that until stabilization. If the blood glucose level was less than 2.2 mmol/L, or at the discretion of the bedside nurse, 25 ml of 50% dextrose was	Glucose meters can be used in a MICU and have a strong correlation with clinical laboratory instruments that are routinely used.

				testing.		administered intravenously.	
DuBose et al. (2012) **LA & Southern California**	Examining the accuracy of capillary blood glucose (CBG) in critically ill trauma patients while they are in the shock state in comparison to laboratory blood glucose (LBG).	A total of 1215 patients were admitted to the ICU. This analysis included 1935 CBG and LBG paired samples in total.		- Capillary blood (fingerstick) (CBG) - glucometer - Peripheral, arterial or central venous blood - central laboratory (LBG)			Following trauma, there is little correlation between the laboratory and capillary glucose readings in the shock and non-shock states. Prior to starting treatment, values obtained through capillary glucose sampling techniques should be verified by laboratory measurements.
Kaukonen et al. (2009) **Finland**	To investigate the prevalence of hypoglycaemia and its effect on patients' outcomes.	A total of 1024 patients.	4–6 mmol/L	Arterial blood gas measurement	Measurements were done at 2hrly intervals		In comparison to earlier trials, severe hypoglycaemiaa during intensive insulin therapy is relatively uncommon in clinical practice. If the advantages of tight glycaemicc control can be verified in additional trials, the risk of hypoglycaemiaa shouldn't prevent the standardized use of intensive insulin therapy.
Thomas et al. (2005) **Salford**	It describes efforts to use a basic web-based insulin dose calculator to improve glycaemic control in critically ill patients.	A total of 891 patients were studied.	Target blood glucose: 5.4 to 7.1 mmol/L.	The use of blood gas analyser and glucometers.	On admission to ICU and then at 08:00 daily by laboratory measurement.	Insulin sliding scales prescribed by the resident medical staff are used to control blood glucose.	We have shown that using an insulin calculator improved glycaemic control in an intensive care unit (ICU) outside of a research setting.

Griesdale et al. (2009) **Canada**	The relationship between serum glucose levels and mortality in individuals with severe traumatic brain injury, were examined. The association between the risk of hypo- and hyperglycaemiaa episodes and mortality were examined.	170 patients.	Maintain blood glucose <10 mmol/L Hyperglycaemia: blood glucose ≥ 11.1 mmol/L. Hypoglycaemia and severe hypoglycaemia: blood glucose ≤ 4.4 mmol/L and ≤ 2.2 mmol/L.		Monitor blood glucose hourly for the first 3 hours. If stable between 4.0 and 10.0 mmol/L, 4hrly monitoring. Otherwise, 2hrly monitoring. If the serum glucose falls below 3.5 mmol/L, 30 min monitoring.		There was no association found between mean morning glucose levels and mortality. A 3.6-fold higher risk of mortality was linked to a single episode of hyperglycaemiaa. Even though the ideal glucose range is still unknown, maintaining serum glucose levels ≤10 mmol/L seems to strike a reasonable balance and may help prevent extremes in glucose values.
Pidcoke et al. (2007) **USA**	Investigations were conducted on patterns of blood glucose and exogenous insulin requirement in the intensive care unit.	156 patients		Readings via point of care monitors.	To create a 24-hour curve, the subjects' hourly blood glucose levels and insulin dosage requirements were matched for the time of day that the measurements were taken.		Insulin levels in healthy subjects are mirrored by the diurnal patterns of insulin requirement in critical injury, which may indicate the persistence of normal variability in insulin sensitivity. Midnight and noontime insulin requirement peaks and troughs, respectively, are probably inversely correlated with typical variations in insulin sensitivity, which peaks during the daytime when energy intake is high.

Chase et al. (2010) **Belgium**	Virtual patients and in-silico virtual trial models and procedures are validated using matched cohorts from a tight glycaemic control clinical trial.	Group A: *n*=124 Group B: *n*=69	Group A: 4.4-6.1 mmol/L Group B: 7.8-10 mmol/L		Hourly blood glucose were recorded when the glycaemic level was not within the target range. 2-hourly measurements in the case of limited variation of glycaemia. 4-hourly when the glycaemic level was less than 50% of the highest glycemia of the four last hours.	A continuous intravenous infusion of insulin was given. Group A: Intensive insulin therapy. Group B: (p4) Conventional insulin therapy.	Overall, this study demonstrates the potential for models to provide accurate, safe, and efficient real-time TGC as well as the capability of model-based, data-driven in silico methods to support protocol design
Holm et al. (2004) **Ireland**	Blood glucose levels were evaluated in patients with severe burns receiving conventional management, and the relationship between early hyperglycaemia and clinical outcome was examined.	37 patients	10 - 11.1mmol/L	Measurement of blood glucose using arterial blood with a glucometer.	Blood glucose levels were taken 8, 16, 24, 36, and 48 hours following the thermal injury.	Maintaining glucose at a level between 10 and 11.1 mmol/L and administering insulin if the blood glucose level rose above 11.9 mmol/L.	Insulin resistance and hyperglycaemia are known to have detrimental effects. Prolonged and early hyperlgycaemia appear to be significant risk factors that may have an adverse effect on survival.
Kulkarni et al. (2005) **Australia**	Analysing the degree of agreement between two blood glucose measurement techniques used on patients in intensive care units: arterial blood using blood gas	54 patients		Arterial blood using a blood gas analyser. Capillary blood using a glucometer.			We conclude that, for a general population of ICU patients, there is statistical agreement between arterial blood gas analysis and blood glucose measured from capillary blood using reagent strips for patients who target a lower limit

	analyser with capillary blood using a reagent strip and glucometer						of blood glucose of 4.4 mmol/l. (p145) We advise using both strategies interchangeably but with caution.

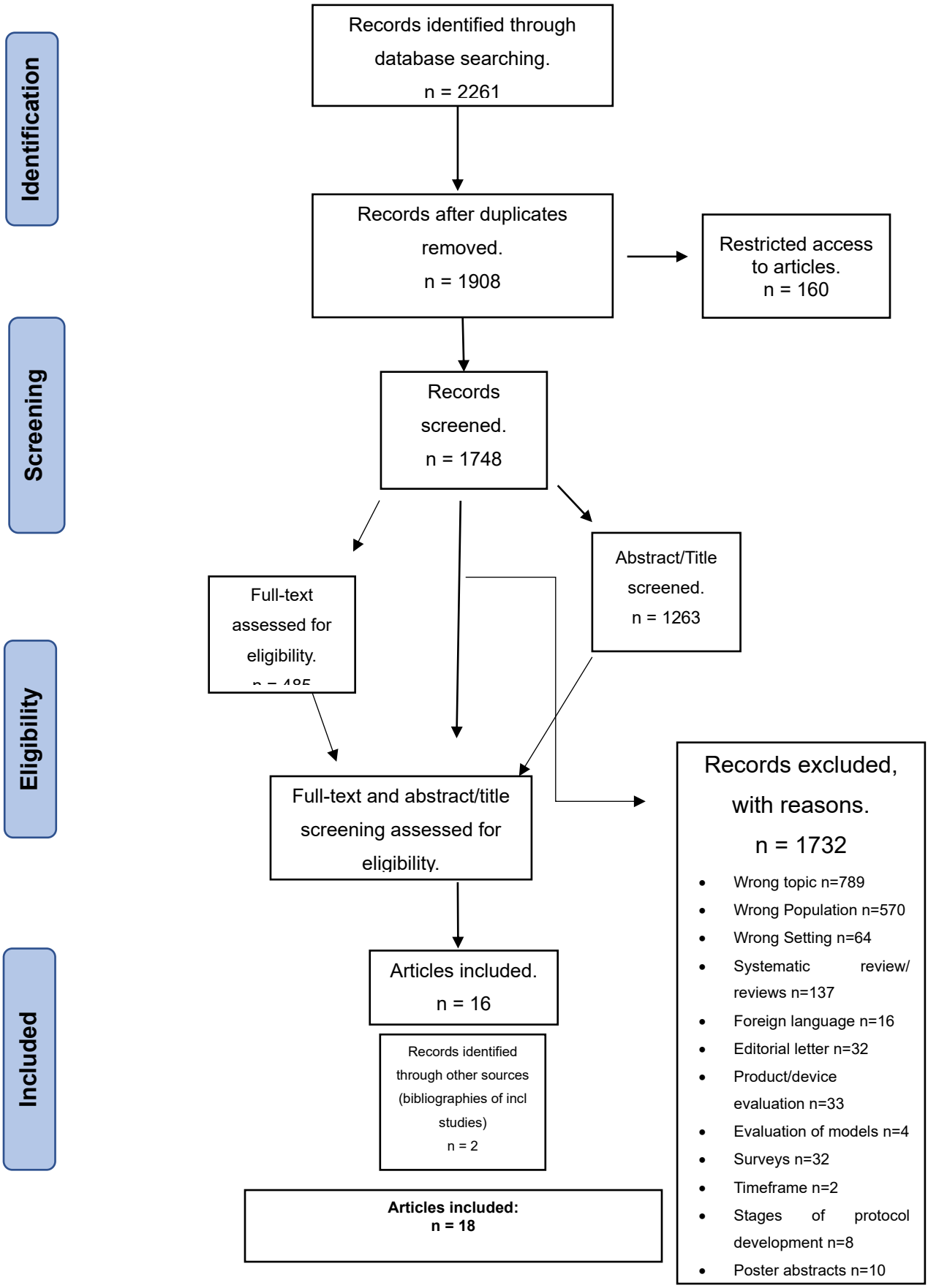
Annexure Ci

Search ID#	Search Terms	Search Options	Last Run Via	Results
S6	((S3) AND (Sl)) NOT (MH "Diabetes Mellitus+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	164
S5	(S3) AND (Sl)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	203
S4	S3	Expande_rs Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	5,963
S3	(MM "Glycemic Control")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	5,963
S2	(MH "Diabetes Mellitus+")	Expande_rs Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	188,681
Sl	(MH "Intensive Care Units+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	69,962

Annexure Cii

Search ID#	Search Terms	Search Options	Last Run Via	Results
S7	((((MH "Intensive Care Units+") OR (MH "Critical Care+")) AND (S2 OR S3)) AND (SI AND S4)) NOT (MH "Diabetes Mellitus+")	Expanders -Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	7
S6	(MH "Diabetes Mellitus+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	496,489
S5	(((MH "Intensive Care Units+") OR (MH "Critical Care+")) AND (S2 OR S3)) AND (SI AND S4)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	11
S4	((MH "Intensive Care Units+") OR (MH "Critical Care+")) AND (S2 OR S3)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	153,666
S3	(MH "Intensive Care Units+") OR (MH "Critical Care+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	153,666

S2	(MH "Critical Illness")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	37,687
Sl	(MM "Glycemic Control")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	741



ANNEXURE D: PRISMA flow diagram of included studies.

ANNEXURE E: University of Pretoria Ethical approval letter

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences

Institution: The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.

- FWA 00002567, Approved dd 18 March 2022 and Expires 18 March 2027.
- IORG #: IORG0001762 OMB No. 0990-0278 Approved for use through August 31, 2023.

Faculty of Health Sciences **Research Ethics Committee**

19 January 2023

Approval Certificate
New Application

Dear Miss L Geldenhuys

Ethics Reference No.: 642/2022
Title: Management strategies of dysglycaemia in critically ill adult patients: a scoping review

The **New Application** as supported by documents received between 2022-11-11 and 2023-01-18 for your research, was approved by the Faculty of Health Sciences Research Ethics Committee on 2023-01-18 as resolved by its quorate meeting.

Please note the following about your ethics approval:

- Ethics Approval is valid for 1 year and needs to be renewed annually by 2024-01-19.
- Please remember to use your protocol number (642/2022) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, monitor the conduct of your research, or suspend or withdraw ethics approval.

Ethics approval is subject to the following:

- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

On behalf of the FHS REC, Dr R Sommers
MBChB, MMed (Int), MPharmMed, PhD
Deputy Chairperson *of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria*

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes, Second Edition 2015 (Department of Health)

ANNEXURE F: Characteristics of sources of evidence *(n=18)*							
Author and publication date	**Study design**	**Population Size [n]**	**Age of population (yrs)**	**Variables measured**			
				Target range of blood glucose	**Sampling method of blood glucose**	**Frequency of blood glucose testing**	**Method of dextrose or insulin administration**
Rodriguez, D.E. et al. (2022)	Prospective cross-sectional study	n=54	Mean: 67.1		●		●
Ellis, M.F. et al. (2013)	Prospective, case-controlled design	n= 50	Mean: 61.3		●		
Mann, E.A. et al. (2011)	Prospective, paired randomization crossover trial	n= 18	Mean: 32	●	●	●	●
Green DM et al. (2010)	Randomized control trial	n=81	Mean: 51	●	●	●	●

Shearer, A. et al. (2009)	Method comparison study design	n=63	Mean: 63.8		●		
Gibson, B.R. et al. (2009)		n=37	Mean: 50-70 for both study groups	●	●	●	●
Graffagnino, C. et al. (2010)	Retrospective before and after study	n=3709	Mean: 53-54 for both study groups	●	●		●
Staszewski J et al. (2011)	Prospective, open-label, single-center, randomized study	n=50	Mean: 68 ± 10	●	●	●	●

Characteristics of the included 18 studies (cont'd)

Author and publication date	Study design	Population Size [n]	Age of population (yrs)	Variables measured			
				Target range of blood glucose	Sampling method of blood glucose	Frequency of blood glucose testing	Method of dextrose or insulin administration

Petersen, J.R. et al. (2008)	Quality assurance project	n=84		●	●		●
DuBose, J.J. et al. (2012)		n=1215	Mean: 38.4	●	●		
Kaukonen, K.-M. et al. (2009)	Retrospective study	n=1024	Mean: 59-61 for both study groups	●	●	●	
Thomas, A.N. et al. (2005)	Service evaluation	n=891	Mean: 51.4	●	●	●	●
Griesdale, D.E.G. et al. (2009)	Retrospective cohort study	n=170	Mean: 38	●		●	●
Pidcoke, H.F. et al. (2007)	Frequency analysis	n=156	Mean: 46		●	●	
Chase, J.G. et al. (2010)	Glucocontrol randomized trial	n=211	Mean: 69-71 for both study groups	●		●	●
Holm, C., Hörbrand, F., Mayr, M., Henckel Von Donnersmarck,	Clinical, prospective, descriptive study	n=37	Mean: 41.2	●	●	●	●

G., Mühlbauer, W. 2004.							
Characteristics of the included 18 studies (cont'd)							
Author and publication date	**Study design**	**Population Size [n]**	**Age of population (yrs)**	**Variables measured**			
				Target range of blood glucose	**Sampling method of blood glucose**	**Frequency of blood glucose testing**	**Method of dextrose or insulin administration**
Kulkarni, A., Saxena, M., Price, G., O'Leary, M.J., Jacques, T. and Myburgh, J.A., 2005.	Prospective, single-centre, observational study	n=54	Mean: 59±17		●		
Bleck TP 2006	Preplanned subgroup analyses of a randomized controlled trial	n=63	Mean: 61	●			