BLOOD GLUCOSE DISTURBANCE IN PATIENTS ENCOUNTERED BY THE EMERGENCY MEDICAL SERVICE

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ACADEMIC DISSERTATION
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“When the unexpected happens,
should you be sweet,
maybe that is too much,
should you not be sweet at all,
that’s even worse,
better to be just yourself”

To Mikko, Iiris, Oskari, Veikka & Anna
ABSTRACT

Background: Blood glucose disturbance is commonly seen in critically ill patients and is associated with a poorer outcome. It has been extensively studied in hospital surroundings. However, blood glucose disturbance can also develop in the prehospital setting. Better knowledge of earlier phases of blood glucose disturbance may help in investigating novel therapeutic interventions and guiding critically ill patients to better medical care.

Aim of the study: To (a) describe how common blood glucose disturbance is in the prehospital setting and its association with short-term mortality and morbidity, (b) describe the very early mechanisms of stress-induced hyperglycaemia, and (c) examine whether blood glucose could be added as an additional parameter to a “track and trigger” scoring system for better discrimination of risk of death.

Materials and Methods: The study consists of four sub-studies. Three of them were retrospective, and one had a prospective study design. We included 152 ST-elevation myocardial infarction patients in the Helsinki city area in 2006-2010 (I), 3568 hypoglycaemic cases without diabetes in the Helsinki University Central Hospital area in 2008-2015 (II), 28 successfully resuscitated out-of-hospital cardiac arrest patients recruited by the two physician-staffed units in Helsinki University Central Hospital area in 2014-2015 (III), and 27141 patient cases with sufficient parameters to calculate the National Early Warning Score and a prehospital blood glucose measurement in the district of Helsinki and Uusimaa in 2009-2015 (IV). In the prospective study, the associations between change in blood glucose and change in insulin, glucagon, and glucagon-like-petide-1 were studied (III). Additionally, changes in blood glucose and hospital admission interleukin-6, cortisol, and HbA1c levels were studied (III). The study time interval was from prehospital blood sampling to hospital admission blood sampling [96 min (IQR 85-119) (III)].

Results: Considering all four sub-studies, hyperglycaemia was present in 76-93% and hypoglycaemia in 2-11% of cases, depending on the study design (I, III, and IV). Diabetes was not previously known in 62-71% of patients (I-IV). Among those patients, 2-11% were considered to have prediabetes (I-III). In patients with ST-elevation myocardial infarction, a greater change in blood glucose from prehospital to hospital admission was associated with 30-day mortality [non-survivors +1.2±5.1 vs survivors -0.3±2.4 mmol/l (mean±SD), p=0.03] (I). Alcohol abuse [41%, (CI95% 40-43)], hypothermia [17%, (CI95% 16-18)], and malnutrition [17%, (CI95% 16-18)] were the most common possible causes of hypoglycaemia (≤3.9 mmol/l)
encountered by the emergency medical service (II). Successfully resuscitated out-of-hospital cardiac arrest patients were found to be hyperglycaemic, with a median blood glucose value of 11.2 mmol/l (IQR 8.8-15.7) after the return of spontaneous circulation and initial resuscitative stabilization (III). Blood glucose decreased by 2.2 mmol/l (IQR -3.6 to -0.2) in the time interval between prehospital blood sampling and hospital admission blood sampling [96 min (IQR 85-119)] (III). Glucagon-like-peptide 1 [6.3 ng/ml, (IQR 5.2-9.0)] increased 2-8-fold from the fasting level. In contrast with previous findings of typical stress-induced hyperglycaemia, prehospital insulin [10.1 mU/l, (IQR 4.2-5.2)] and glucagon [141 ng/l, (IQR105-240)] levels were low (III). The biomarkers insulin, glucagon, glucagon-like-peptide-1, interleukin 6, and cortisol had great interindividual variation, and this outcome was not associated with a change in blood glucose level (III). A multivariate regression model for the National Early Warning Score with blood glucose as an additional parameter revealed that hyperglycaemia moderately [24-hour risk of mortality: OR 1.54, (1.11-2.12) and 30-day risk of mortality: OR 1.41, (1.20-1.66)] and hypoglycaemia strongly [24-hour risk of mortality: OR 5.46, (2.87-9.64) and 30-day risk of mortality: OR 2.33, (1.47-3.52)] improved the discrimination of risk of death (IV). The association was improved according to likelihood ratio tests (p<0.001). Reclassification tests additionally confirmed the improvement of the model. Continuous net reclassification index at 24-hours risk of mortality was 0.413, CI95% 0.281-0.545, p<0.001; at 30-days risk of mortality it was 0.254, CI95% 0.197 -3.11, p<0.001; and integrated discrimination improvement was at 30-days risk of mortality 0.002, CI95% 0.001-0.003, p<0.001. Risk per point estimation and calibration confirmed the benefit for better discrimination of risk of death at 24 hours and at 30 days.

**Conclusions:** Disturbance of blood glucose homeostasis was commonly observed already in prehospital surroundings and seemed to be associated with an elevated mortality risk during critical illness. When added as an additional parameter to the National Early Warning Score, especially when hypoglycaemia was present, discrimination of risk of death seemed to be improved. In contrast with the insulin resistance and excess counterregulatory hormones typically seen in stress-induced hyperglycaemia, the initial physiological mechanisms of blood glucose disturbance seemed to differ because both insulin and glucagon levels were found to be initially low.
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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which will be referred to in the text by Studies I to IV.


ABBREVIATIONS

ACS  acute coronary syndrome
ADA  American Diabetes Association
AUROC area under the receiver operating curve
Chip  Control of hyperglycaemia in paediatric intensive care
CI95%  95% confidence interval
cNRI  continuous net reclassification index
CNS GLP-1 glucagon-like-peptide 1 secreted from the brain
CREATE-ECLA The Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment and Evaluation -Estudios Clínicos Latino América
DIGAMI I Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction trial I
DIGAMI II Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction trial II
ECG  electrocardiogram
ED  emergency department
EMA  European Medicine Agency
EMS  Emergency medical service
GIK  glucose-insulin-potassium
GIP  glucose-dependent insulinotropic peptide
GDH  glucose dehydrogenase
GIPS-1 Glucose Insulin Potassium Study-1
GIPS-2 Glucose Insulin Potassium Study-2
GLP-1 glucagon-like-peptide-1
GLUT-1 glucose transported protein type 1
GLUT-4 glucose transported protein type 4
GOD  glucose oxidase
GRACE Global Registry of Acute Coronary Events
HALF-PINT Heart and lung failure paediatric insulin titration trial
HEMS  Helicopter Emergency Medicine Service
HI-5 study  Intensive Insulin Infusion in Infarction study
HOMA-index homeostatic model assessment-index
HUCH Helsinki University Central Hospital
ICU  intensive care unit
IDI  integrated discrimination improvement
IL-1 interleukin-1
IL-6 interleukin-6
IQR  inter quartile range
ISS  injury severity score
IMMEDIATE  Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency Care
MODY  maturity-onset diabetes of the young
NEWS  national early warning score
NEWSgluc  new model of national early warning score with the addition of blood glucose as a parameter
NICE-SUGAR  Normoglycaemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation
NIPHS  Noninsulinoma pancreatogenous hypoglycaemia syndrome
non-STEMI  non-ST-elevation myocardial infarction
OASIS-6  Organization for the Assessment of Strategies for Ischaemic Syndromes-6
OHCA  out-of-hospital cardiac arrest
PCI  percutaneous coronary intervention
PEDS  Prince of Wales Emergency Department Score
RCT  randomized controlled trial
SIH  stress-induced hyperglycaemia
SIH-ACS  SIH-acute coronary syndrome
SOAR  Oxford community Stroke Project classification, age, and prestroke modified Ranking
SPECS  Safe Paediatric Euglycaemia after Cardiac Surgery
STEMI  ST-elevation myocardial infarction
TNF-alpha  tumour-necrosis-factor alpha
1 INTRODUCTION

Blood glucose disturbance is often seen in critically ill patients, such as those with ST-elevation myocardial infarction (STEMI), cardiac arrest, stroke, traumatic brain injury, and sepsis. It typically resolves after recovery from illness. Constant energy, especially to the brain, is mandatory for sustaining life. To sustain energy influx, complex humoral and neuronal feedback mechanisms have evolved to maintain prandial blood glucose homeostasis between 4.4 and 7.0 mmol/l.

Evolution has also made it possible for ancestors to survive minor, but not major, injuries and infections, when they were hunting or facing a threat in their daily lives by increasing the blood glucose level via changes in metabolic pathways. However, modern medicine has made it possible to survive severe conditions that might otherwise have led to death. The evolvement of intensive care medicine and advanced age have turned this evolutionary survival mechanism against the body, and hence it has become a pathological reaction. Many studies have found a harmful association between poor outcome and blood glucose disturbance during critical illness, and it can affect both patients with and without diabetes.

Blood glucose disturbance may present as stress-induced hyperglycaemia (SIH) or spontaneous hypoglycaemia. SIH acts via the hypothalamus-pituitary axis through complex inflammatory mechanisms leading to insulin resistance and an excess of the counterregulatory hormones glucagon, epinephrine, growth hormone, and cortisol. Spontaneous hypoglycaemia can develop instead of SIH. It is thought that in spontaneous hypoglycaemia, insufficient amounts of counterregulatory hormones are secreted by the body in relation to insulin secretion and action.

This study may help in investigating novel therapeutic interventions, which could be implemented earlier in the prehospital setting and hence may yield better patient care during critical illness. Blood glucose is a simple biomarker that is routinely recorded by the EMS. Hence, it might be useful to add blood glucose to the widely used “track and trigger” system, the National Early Warning Score (NEWS).

The aim of this study was to describe how common blood glucose disturbance is in hypoglycaemic patients without diabetes in the prehospital surroundings, how it is associated with STEMI and OHCA patients in the prehospital surroundings, and determine whether there are differences in the early physiological mechanisms behind SIH after OHCA compared with the known typical development of insulin resistance and excess of counterregulatory hormones, and assess whether blood glucose should be used as part of the “track and trigger” system, National Early Warning System.
2 REVIEW OF THE LITERATURE

2.1 Regulation of blood glucose

2.1.1 Normal blood glucose metabolism and diabetes

Blood glucose homeostasis is meticulously balanced by complex neuronal and metabolic pathways in cells to maintain preprandial glucose between 4.4 and 7.0 mmol/l. Humoral feedback mechanisms are regulated by the glucoregulatory hormones insulin, glucagon, epinephrine, growth hormone, cortisol, amylin, leptin, and ghrelin and by the incretin hormones glucose-dependent insulinotropic peptide (GIP) and glucagon-like-peptide-1 (GLP-1). The gut-brain axis is part of blood glucose homeostasis regulation. In addition to hormonal regulation, the liver functions via neuronal feedback mechanisms sensed from glucosensors in the body and is capable of adjusting glucose production and output through autoregulation.

For sustaining vital brain functions and preserving life, a constant glucose supply is mandatory. Basal cell glucose utilization is mediated by glucose transport carrier protein 1 (GLUT-1), an insulin-independent carrier protein, in a concentration-dependent manner. This is called the mass-effect of glucose. GLUT-1 is especially highly expressed in the endothelial cells of the blood-brain-barrier neuronal and in the erythrocytes. The rate of GLUT-1 expression is regulated by substrate availability, by the energy state of the cell, and by presence of glycolytic products such as glucose-6-phosphate. In skeletal muscle cells, myocardial cells, and adipose tissue cells, glucose is also transported to cells via the insulin-dependent transport carrier protein called glucose transport protein 4 (GLUT-4).

After a meal, the rise in blood glucose initiates rapid insulin secretion. In the first minutes, the body rapidly depletes preformed insulin storages from pancreatic beta-cells in the islets of Langerhans, which causes a rapid initial peak in the basal insulin level. Approximately 15 minutes after ingestion of the meal, newly produced insulin is secreted, which causes a second, longer insulin secretion peak lasting approximately three hours. Insulin is the primary postprandial hormonal regulator, and it functions by mediating glucose uptake into skeletal muscle, myocardial, and adipose tissue cells via GLUT-4. At the same time, insulin inhibits glucagon secretion from pancreatic alpha cells, thereby hindering glycogenolysis and gluconeogenesis. The incretin hormones GIP (secreted from K-cells) and GLP-1 (secreted from L-cells) in the intestine are highly secreted...
after a meal. GLP-1 is synthesized from a preglucagon precursor via gene sequence coding. GLP-1 is more active in insulin-dependent processes, and GIP is more active in non-insulin-dependent processes. GLP-1 increases insulin secretion 2-3-fold after a meal, inhibits glucagon secretion in a glucose-dependent manner and slows gastric emptying and motility, thus promoting a more balanced rise in blood glucose concentrations. Actions of GIP differ from GLP-1. GIP stimulates glucagon secretion in the fasting state, although not during hyperglycaemia, and it does not affect gastric emptying. A simplified figure illustrating regulation of glucose homeostasis is presented in Figure 1.

Figure 1. Simplified illustration of glucose homeostasis regulation.

Glycogenesis=formation of glycogen storages; Glycogenolysis=glucose generation from glycogen storages; Gluconeogenesis=a metabolic pathway through which glucose is generated from amino-acids, lactate, or free fatty acids; GIP=gastric inhibitory peptide; GLP-1=glucagon-like-peptide 1.

Amylin is secreted from the pancreatic beta cells of the islets of Langerhans, along with insulin. Its main action is to enhance glucoregulatory actions by suppressing glucagon secretion, slowing gastric emptying, and causing satiety. Leptin acts more centrally in the hypothalamus through a non-insulin-mediated mechanism and takes part in enhancing the overall mechanisms of blood glucose. Ghrelin functions by increasing appetite and food intake in starvation conditions, by increasing gastric acid secretion and motility, by inhibiting insulin and leptin secretion, and by increasing endogenous GLP-1 secretion.
When aerobic conditions are present, glucose is primarily converted into energy in the mitochondria via oxidative phosphorylation by the Krebs cycle (Figure 2) \(^{30}\). An alternative metabolic pathway is glycolysis, which is capable of producing energy under anaerobic conditions. Glycolysis is one hundred times faster, although it yields only 5% of the total energy compared with oxidative phosphorylation \(^{41}\). In glycolysis, glucose is converted to pyruvate and then to lactate, which is reconverted to glucose in the liver and kidney through the Cori cycle. \(^{30}\) A third metabolic pathway for glucose also exists in cells \(^{30}\). This pathway is called the pentose phosphate pathway, which is more of an anabolic pathway because it uses glucose to produce nucleotides and intermediates that help counteract oxygen radical reactions \(^{30}\). Substrate availability (glucose, lactate, free fatty acids and amino acids), not the current blood glucose level, is the rate-limiting step for these metabolic pathways and for glycogen storage \(^{42}\). This substrate availability is monitored by central and peripheral glucosensors in the body, which are involved in neural glucoregulation and liver autoregulation, and via feedback mechanisms of hormonal responses \(^{43}\).

**Figure 2.** Metabolic pathways of glucose metabolism \(^{30,44}\).

GLUT-1=glucose transport protein; Glycogenesis=formation of glycogen storages; Glycolysis=an oxygen-independent metabolic pathway in which glucose is converted into 2 pyruvates, forming lactate and energy; Gluconeogenesis=metabolic pathway in which glucose is generated from precursors: amino acids, lactate, or free fatty acids; Pentose phosphate pathway=an oxygen-independent metabolic pathway that generates nucleotides; Glycogenolysis=glucose formation from glycogen storages; Lipolysis=degradation of triglycerides to glycerol and free fatty acids; Lipogenesis=formation of triglycerides from glycerol and free fatty acids; Ketogenesis=formation of ketone bodies from excess of Acetyl-CoA.
During basal conditions, when normoglycaemia is present, non-insulin mediated glucose uptake dominates, which results in the central nervous system, especially the brain, to uptake 80% of circulating glucose. After a meal, insulin-mediated glucose uptake is increased, which results in increased glucose uptake more into skeletal muscles. The glucose is used in the cell directly as a fuel or stored in the body as glycogen. Excess amounts of glucose are converted into triglycerides. Approximately 10% of the liver glycogen storage is produced as follows. After a meal, in skeletal muscle cells, approximately 10% of absorbed glucose is converted into lactic acid through anaerobic glycolysis, which then enters the circulatory system and liver cells where it is converted into glycogen. Neuronal cells of the brain, primarily glial cells, can also store glycogen. These neuronal glycogen storages are small but important because with these storages the brain is capable of preserving an energy supply for 4-5 min if the constant glucose supply is disturbed.

A decrease in blood glucose level by 0.6-0.8 mmol/l or to 4.4 mmol/l is sufficient to cause cessation of insulin secretion. This is the first mechanism of glucose counterregulation. When the blood glucose level falls and insulin secretion does not occur, glucagon secretion is increased. Glucagon is the main counterregulatory hormone, and it functions by releasing glucose first from the liver and later from kidney and muscle cells via glycogenolysis. At the same time, glucagon promotes gluconeogenesis from amino acids, lactate, and free fatty acids. Growth hormone and cortisol also take part in elevation of blood glucose concentrations, but they act slower. Their function is to inhibit cell utilization of glucose and increase lipolysis, which enhances gluconeogenesis through increased substrate availability. Epinephrine may not be needed under normal conditions. However, when glucagon is not present, the actions of epinephrine become critical. Epinephrine promotes glycogenolysis in kidney and skeletal muscle cells during stress and inflammation. In contrast with glucagon, epinephrine also decreases glucose utilization in cells.

When liver glycogen storages are depleted during fasting conditions, lipolysis is increased. Formed free fatty acids are converted in the mitochondria into Acetyl-CoA via beta-oxidation, which enters the Krebs cycle to form additional energy. When excess amounts of acetyl-CoA are produced from free fatty acids, the capacity of the Krebs cycle is exceeded. Instead of entering the Krebs cycle, the excess acetyl-CoA is then converted into ketone bodies. Liver cells are not capable of using these ketone bodies as an energy source, and thus, they enter the circulatory system and the brain, where they can be used as an alternative energy source during a prolonged imbalance in glucose homeostasis. Insulin functions by inhibiting lipolysis and ketogenesis, and glucagon increases ketone body formation by supplying increasing amounts of free fatty acids.
During high energy demand, such as during strenuous exercise, the metabolic pathway shifts towards glycolysis, producing lactate and hydrogen ion (H+) in cells. However, inflammatory conditions or actively reproducing cells may cause a higher energy demand, although a sufficient oxygen supply is present. This phenomenon is called the Warburg effect. The formed lactate and hydrogen ions enter the circulatory system causing lactic acidosis. Under physiological conditions, lactate is not excreted from the kidney. However, when lactate concentrations are greater than 5-6 mmol/l, renal excretion of lactate occurs. Acidotic conditions inhibit gluconeogenesis in the liver and increase gluconeogenesis in the kidney. When aerobic conditions are again present, lactate is turned back into glucose via glycolysis through the Cori cycle.

Diabetes mellitus is a heterogenous disease in which blood glucose homeostasis is chronically disturbed. It may be due to autoimmune reactions in pancreatic beta-cells or to genetic and environmental factors of various degrees. This results in absolute insulin deficiency or decreased insulin action in tissues, causing insulin resistance (Figure 3).

Diabetes mellitus is classified into four categories by the American Diabetes Association (ADA): type 1 diabetes, type 2 diabetes, gestational diabetes, and specific types of diabetes due to other causes. Type 1 diabetes is caused by an autoimmune reaction of beta-cells leading to absolute insulin deficiency. In type 2 diabetes, there is progressive loss of beta-cell insulin secretion along with increased insulin resistance. Gestational diabetes is diagnosed in the second or third trimester of pregnancy in patients who have no previous diabetes diagnosis. This type of diabetes resolves after pregnancy. However, the individual is at higher
risk for developing type 2 diabetes later on. The last category consists of diabetes developed due to various causes: after drug induction (such as glucocorticoid use), disease-related diabetes (such as complication from pancreatitis or cystic fibrosis), or from monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young (MODY)). However, sometimes patients cannot be initially characterized as having a specified type of diabetes because it is a very heterogeneous disease.

2.1.2 Stress-induced hyperglycaemia (SIH)

Hyperglycaemia, a compensatory mechanism for survival, is common during critical illness. Depending on research data, 38-97% of critically ill patients have elevated blood glucose concentrations. SIH is a condition seen in patients both with and without diabetes, and it typically resolves after acute illness and is associated with a poorer outcome. According to the American Diabetes Association (ADA), SIH is defined as a transient condition with a spontaneously elevated random blood glucose level of 11.1 mmol/l or above, an elevated fasting glucose level of 7.0 mmol/l or above, or an HbA1c concentration of 6.5% or above in a well-balanced diabetes patient during critical illness. However, due to heterogeneous study designs and conflicting results, there is currently no international consensus on a specific definition or on when SIH should best be targeted for treatment.

The magnitude of the underlying mechanisms of SIH likely varies based on the severity and stage of illness and the patient age and characteristics. Vasopressors, parenteral nutrition, and corticosteroids aggravate the pathophysiological mechanisms of SIH. Patients with diabetes already have chronically disturbed body metabolism due to metabolic derangements caused by diabetes. This affects the pathophysiological mechanisms of SIH. Krinsley et al. found that patients without diabetes treated in the ICU had a 4.5-fold higher risk of death than diabetics when blood glucose was 11.1 mmol/l or more. Therefore, it has been suggested that patients with and without diabetes should have different treatment target glucose level ranges. Overall, critical illness itself may directly lead to new-onset diabetes.

The underlying mechanisms involve neuroendocrine and humoral changes causing sympathetic nervous system and hypothalamic-pituitary-axis activation promoted by complex inflammatory cascades, which are enhanced by the shift in glucose regulation homeostasis toward glycolysis causing increased lactate substrate availability (Figure 4). Stress causes inflammatory changes in the body, which is seen as elevated concentrations of the cytokines interleukin 1 (IL-1), interleukin 6 (IL-6), and tumour necrosis factor alpha (TNF-alpha).
IL-6 is thought to increase GLP-1 secretion \(^\text{75}\). During severe stress, such as in cardiac arrest, epinephrine secretion from the adrenal medulla can increase up to 1000-fold, causing a hyperstimulatory condition in the body and leading to highly increased glycogenolysis, gluconeogenesis, and lipolysis \(^\text{76}\). An increased lactate level causes downregulation of GLUT-4 in myocardial, skeletal muscle, and adipose tissue leading to decreased insulin sensitivity in the tissues \(^\text{77}\). At the same time, GLUT-1 expression is upregulated, leading to increased glucose uptake in the brain and other GLUT-1-dependent cells through a non-insulin mediated mechanism \(^\text{6,24,78}\). Hence, less glucose reaches insulin-dependent cells although a sufficient amount of insulin is available; a condition called insulin resistance develops. As a consequence, the body increases glucagon, epinephrine, cortisol, and growth hormone secretion so additional glucose can be produced for the cells \(^\text{24}\). Glycogenolysis and gluconeogenesis in the liver and kidney are increased along with increased substrate availability via glycolysis (lactate), lipolysis (free fatty acids) and proteolysis (amino-acids). Free fatty acids are released in excess into the circulatory system, which leads to formation of circulating ketone bodies. Ultimately, the imbalance in regulation of glucose homeostasis enhances a hypermetabolic state, which is seen as increasing hyperglycaemia, hyperlactatemia, and excess of circulating free fatty acids \(^\text{14}\). In the end, SIH causes endothelial dysfunction, immune dysregulation, free oxygen radicals, arrhythmias, impaired fibrinolysis, platelet activation, electrolyte disturbances and eventually death \(^\text{79,80}\). Complications, such as a longer hospital stay, prolonged mechanical ventilation, a transfusion requirement, polyneuropathy, and sepsis, may precede these morbid complications \(^\text{14}\).

Incretin hormones, GLP-1 and GIP, are primarily secreted from the small intestine, although small amounts of GLP-1 are also secreted from the central nervous system \(^\text{86}\). During critical illness, secretion of GLP-1 and GIP increases over 6-fold \(^\text{87-89}\). The target organs of intestinally secreted GLP-1 are the pancreas, central nervous system, heart, lung, kidney, thyroid gland, and stomach \(^\text{90}\). In the pancreas, GLP-1 causes increased insulin secretion and inhibition of glucagon secretion; in the stomach, it inhibits gastric emptying; and in the heart, it improves cardiac function \(^\text{91-94}\). The action of GLP-1 in the thyroid gland, kidney, and lung is not within the scope of this review. CNS GLP-1, secreted from the brain, affects anticipation and regulation of stress behaviour and induces satiety \(^\text{86}\). Endogenous GLP-1 has a very short half-life \(^\text{95}\). Therefore, a continuous infusion is needed when used for treatment. Hence, GLP-1-analogues have been developed, which have a longer half-life.
Counter-regulatory hormones are produced in excess: Glucagon (fast action), Epinephrine (fast action), growth hormone (slow action), Cortisol (slow action).

**STRESS FROM CRITICAL ILLNESS**

Cytokines (TNF-α, IL-1, and IL-6) are produced in macrophages, monocytes, and endothelial cells.

Adipose tissue

Insulin production increases and glucagon secretion is inhibited.

Metabolic pathways shift more to glycolysis

Decreased substrate availability

Non-insulin mediated glucose intake by GLUT-1 upregulation increased

Increased glycogenolysis and gluconeogenesis

Figure 4. Illustration of physiological mechanisms of SIH 6,8,19,24,34,72–85; GLP-1=glucagon-like-peptide 1; TNF-α=tumour necrosis factor alpha; IL-1=interleukin 1; IL-6=interleukin 6; GLUT-4=glucose transporter protein type 4.

2.1.3 Spontaneous hypoglycaemia

Spontaneous hypoglycaemia is defined by hypoglycaemia presented with no obvious cause and fulfilment of Whipple’s triad: blood glucose level 3.0 mmol/l or less, autonomic and neuroglycopenic symptoms, and resolution of the condition by giving glucose 96,97. It may affect patients with diabetes or without diabetes. Endocrinological disorders; post-gastric bypass surgery; certain tumours (insulinoma and insulin growth factor secreting tumours); and rare disorders, such as noninsulinoma pancreaticogenous hypoglycaemia syndrome (NIPHS) or insulin autoimmunity, may be the cause of hypoglycaemia when diabetes is excluded 98. In critical illness, spontaneous hypoglycaemia is a sign of already gravely compromised homeostasis of the body and is associated with high mortality 98,99. Risk factors for hypoglycaemia are increased age and recurrent hospitalization as well as imbalanced diabetes mellitus 100,101. In addition, renal failure, liver failure, and female sex are risk factors 98,102. Liver failure causes inability of the liver to adequately replenish liver glycogen storages via gluconeogenesis. Renal failure reduces insulin clearance and gluconeogenesis in the kidney 103.

Spontaneous hypoglycaemia is not common because the body has evolved a strong defence mechanism to prevent hypoglycaemia 93. As a first line of defence, the
body inhibits insulin secretion when the blood glucose level decreases 0.6-0.8 mmol/l or to a preprandial level of 4.4 mmol/l \(^{49-51}\). Second, glucagon secretion is increased as blood glucose further decreases to 3.9 mmol/l or less, and if this is not sufficient, epinephrine is secreted from the medulla to enhance counterregulation of hypoglycaemia \(^{49-51}\). These hormonal counterregulatory mechanisms are activated at higher blood glucose levels than, when hypoglycaemia symptoms occur (≤3.3 mmol/l) \(^{49-51}\). As hypoglycaemia develops further the sympathetic nervous system is activated causing typical hypoglycaemia symptoms \(^{104}\) (Figure 5). These symptoms are divided into autonomic and neuroglycopenic symptoms. Autonomic symptoms appear first and are further divided into adrenergic and cholinergic symptoms \(^{105,106}\). Adrenergic symptoms are tachycardia, anxiety, dilated pupils, and tremor. Cholinergic symptoms are nausea, sweating, and hunger. Neuroglycopenic symptoms with cognitive dysfunction are seen when an adequate glucose supply is not delivered to the brain and the local neuronal glycogen storages have been depleted. At this point, the blood glucose level is 2.8 mmol/l or less \(^{27,69,7}\). Neuroglycopenic symptoms cause behavioural changes, amnesia, vision changes, clumsiness, ataxia, slurred speech, headache, seizure, and loss of consciousness \(^{104}\). As hypoglycaemia is prolonged, cortisol and growth hormone takes part in the counterregulatory defence mechanisms against hypoglycaemia \(^{34}\). When hypoglycaemia is severe, the liver can free glucose from its own glycogen storages without counterregulatory hormone stimuli \(^{34}\). This is part of the autoregulation of the liver \(^{20}\).

**Figure 5.** Development of hypoglycaemia symptoms and counterregulatory actions against hypoglycaemia \(^{49-51}\).

Autonomic nervous system symptoms=sweating, dilated pupils, hunger, nausea, and tachycardia; Neuroglycopenic symptoms=abnormal thinking, irritability, anxiety, slurred speech, clumsiness, headache, paraesthesia, paralysis, fatigue, seizures, and unconsciousness.
In spontaneous hypoglycaemia, insulin secretion is inhibited, and one or more of the counterregulatory hormones, such as glucagon, epinephrine, growth hormone, or cortisol, are insufficiently able to maintain blood glucose at normoglycaemia (Figure 6) \(^{15}\). The high energy demand in critical illness shifts the energy balance to glycolysis, causing increased lactate production \(^{71–73}\). As a result, the decreased supply of glucose into the cells causes increased lipolysis and circulating free fatty acids, as in SIH. \(^{15}\). These pathophysiological mechanisms, including increased catecholamine levels, increased inflammatory markers and free circulating fatty acids, cause cerebral vasodilation, platelet aggregation, endothelial dysfunction, and arrhythmias (Figure 5) \(^{107–109}\). A study by Lang CH et al. confirmed that a 2 mmol/l reduction in blood glucose level increased glucose uptake to cells by 40–45\%, further aggravating hypoglycaemia \(^{110}\). Overall, hypoglycaemia is an imbalance in relative insulin excess compared with counterregulatory hormone levels, resulting in an excess of circulating free fatty acids, increased glucose uptake, and an enhanced systemic inflammatory response \(^{14}\). These factors cause cerebral vasodilatation, arrhythmias and brain damage, eventually leading to death \(^{105}\). The brain is especially vulnerable to hypoglycaemia \(^{11,111}\).

Figure 6. Development of spontaneous hypoglycaemia.

2.1.4 Blood glucose disturbance in acute coronary syndromes (ACS)

Acute coronary syndromes includes STEMI, non-ST-elevation myocardial infarction (non-STEMI), and unstable angina \(^{112}\). SIH and spontaneous hypoglycaemia may both develop during ACS \(^{24,113,114}\).

During acute myocardial infarction, the catecholamine level increase due to pain and distress, causing tachycardia and an increased demand for energy, which
enhances glycolysis and glycogenolysis\textsuperscript{14,115}. Myocardial cells primarily use free fatty acids as an energy fuel under normal conditions\textsuperscript{116,117}. However, in the ischaemic myocardium, glucose intake is increased because the ischaemic myocardium uses glucose for glycolysis as an energy substrate\textsuperscript{118}. At the same time, GLUT-4 expression is downregulated to prevent too much glucose intake into the ischaemic myocardium\textsuperscript{77}. Typical pathophysiological mechanisms of SIH start developing, with insulin resistance and excess of counterregulatory hormones, along with complex inflammatory cascades (Figure 7). Increased glycolysis produces lactate and H\textsuperscript{+}\textsuperscript{1} ions, which start to accumulate\textsuperscript{71–73}. This causes toxic effects in the ischaemic myocardium\textsuperscript{119}. At the same time, glucoregulatory hormones enhance lipolysis, resulting in free fatty acid accumulation in the circulatory system\textsuperscript{56}. These free fatty acids cannot be used in the ischaemic myocardium due to mitochondria damage caused by ischaemia\textsuperscript{71}. Excess of free fatty acids are toxic to the myocardium through several mechanisms. They cause direct cell injury\textsuperscript{120}; they increase oxygen demand\textsuperscript{71}; and they inhibit glucose oxidation in the myocardium\textsuperscript{121}. Excess glucose and free fatty acids in the circulatory system cause increased platelet aggregation, fibrinolysis, coagulation disturbances, endothelial dysfunction, and vasodilation, leading to impaired microcirculation\textsuperscript{80,122–125}. This can be seen as a no-flow phenomenon after percutaneous reperfusion therapy\textsuperscript{80}. Hence, the actual PCI may be successful, but due to impaired microcirculation, the patient outcome does not improve\textsuperscript{80}.

**Figure 7.** Illustration of pathophysiological mechanisms of SIH in an ischaemic heart\textsuperscript{19,30,80,122–126}. 
Although myocardial cells seem to have a self-protective mechanism against excess nutrition, the pathophysiological mechanisms of SIH, along with free fatty acids as a side product, directly damage the heart, which can be seen as a larger infarct size, electric instability, impaired left ventricular function, and increased cardiac enzyme markers 80,120,127. The myocardial ejection fraction may also decrease during ischaemic conditions, resulting in diminished output of the heart and less peripheral circulation 128. Hence, less oxygen is delivered into the tissues, causing more anaerobic conditions, further enhancing inflammatory cascades and anaerobic glycolysis, increasing lactic acidosis, and thereby inducing more severe SIH 129.

If spontaneous hypoglycaemia develops, compensatory mechanisms for survival were not able to compensate adequately to the stress demand of critical illness caused by myocardial ischaemia 98. Although, insulin actions are more responsible than counterregulatory hormone actions for causing hypoglycaemia, spontaneous hypoglycaemia also further increases epinephrine secretion and sympathetic nervous system action as a defence mechanism. Hence, hypoglycaemia provokes tachycardia, catecholamine-mediated hypokalemia, flattening or inversion of T-waves, ST segment depression, and QT-interval prolongation up to 580 ms in the electrocardiogram; disturbances which can lead to arrhythmias 130. Spontaneous hypoglycaemia leads to denser thrombin formation by increased inflammatory reactions, by endothelial dysfunction, by hindering fibrinolysis, and by increasing platelet activation 130. Simultaneously excess of circulating free fatty acids eventually damaging more the myocardium, as in SIH 15.

2.1.5 Blood glucose disturbance in out-of-hospital cardiac arrest (OHCA)

Out-of-hospital cardiac arrest (OHCA) has an incidence of 51 per 100 000 inhabitants per year in Finland 131. Major metabolic disturbances are caused by direct ischaemic injury and through secondary reperfusion injury 132–134. Hence, a sepsis-like condition called post-cardiac arrest syndrome develops 135. Although arrest duration and the quality of post-resuscitation care is associated with the degree of blood glucose disturbance, the post-cardiac arrest syndrome that develops does not completely explain the mechanisms behind blood glucose disturbance 136. After a global ischaemic insult, the body may be stunned by global ischaemia. However, it is known that TNF-alpha and IL-1 cause GLUT-1 to be upregulated resulting in non-insulin-mediated glucose uptake to be increased in cells 6,137,138. It is thought that glucagon is not very active at this point 139. Instead, epinephrine is highly secreted, causing hyperglycaemia via glycogenolysis in the liver, skeletal muscle cells, and especially in the kidney 34,76. Under severe stress, such as after cardiac arrest, the kidney increases its gluconeogenesis ability, producing more than...
30% of the body's new available glucose. Body metabolism is shifted towards anaerobic glycolysis in hypoxic areas of the body with increasing energy demand. At the same time, in the ischaemic areas of the body, mitochondrial dysfunction causes further impairment of energy metabolism homeostasis. Eventually, SIH develops with typical characteristics, along with complex inflammatory cascades, insulin resistance and excess of counterregulatory hormone secretion, which promotes more glycogenolysis in the liver, kidneys, and skeletal muscles and gluconeogenesis in the liver and kidney (Figure 8). Free fatty acids formed via lipolysis promoted by counterregulatory hormones start circulating in excess and cannot be sufficiently used by the body due to mitochondrial dysfunction. Altogether, substrate availability is the rate-limiting step for changes in metabolic pathways. This means that glucose, lactate, and free fatty acid substrate availability have a greater effect on metabolic changes than the specific blood glucose level. When counterregulation is not sufficient, spontaneous hypoglycaemia develops instead of SIH.

Figure 8. Timeline of initial pathophysiological mechanisms of blood glucose disturbance in OHCA.

OHCA=out-of-hospital cardiac arrest; IL-1= interleukin 1; IL-6= interleukin 6; TNF-alpha; GLUT-1=glucose transporter protein type 1; GLUT-4=glucose transporter protein type 4; ICU=Intensive Care Unit; SIH= Stress-induced hyperglycaemia.
2.2 Blood glucose measurement

Point-of-care testing is often measured from a finger-tip capillary sample, but it may also be carried out with arterial or venous blood. The point-of-care method is often used by the EMS and in hospital wards. For accurate results, calibration frequency, sampling and measurement need to be standardized.

The results are often interpreted as accurate although there are discrepancies. However, many things may cause artefacts that affect the results. Previously, a 20% difference between two samples was agreeable. Currently, the accepted difference has been narrowed to 15%\(^145\). To guarantee this, the blood glucose metres should fulfil minimum requirements by using EN ISO 15197:2015 criteria; 95% of the results should be ±0.8 mmol/l of the averaged measured values\(^145\). Glucometer strips contain enzymes that react to hexoses such as glucose, and to other hexoses, fructose, maltose, mannitol, and lactose. Hence, other hexoses may cause artefacts. In some strips, glucose oxidase (GOD) is used. This enzyme is known to interact with, for instance, the haematocrit, giving false blood glucose results. Glucose dehydrogenase (GDH) has now replaced GOD in many glucometers and gives more accurate results.

Patient characteristics, such as hypotension, oedema and vasoconstriction causing low peripheral blood flow, may affect blood glucose results\(^146-147\). A high haematocrit may cause falsely low blood glucose values, and vice versa, although newer glucometers are designed so that the haematocrit values does not affect the blood glucose results\(^148-159\). Extreme acidosis or alkalosis may also affect the accuracy of blood glucose results\(^151\).

Climate factors may also affect the accuracy of blood glucose results. For example, differences in altitude, temperature, and humidity may affect the accuracy of blood glucose measurements\(^152,153\). Medications, such as paracetamol, ascorbic acid, and salicylate, as well as dopamine and non-glucose hexoses are known to cause artefacts that affect the blood glucose measurement\(^154-155\). However, the development of new glucometers has been fast in recent years. In newer glucometers, these artefacts are taken into account, and the new glucometers give more accurate blood glucose results, although they are not yet sufficiently accurate for patients with critical illness\(^156\).

The most accurate results are obtained from arterial or venous blood samples, which are used in the intensive care units. Sensors are a new option, but they also have limitations. Direct measurement from arterial blood by sensors seems to be very accurate, but this sophisticated method is not suitable for prehospital
surroundings or general wards. Point-of-care sensors have become very popular as a self-measurement tool in diabetes. However, during critical illness due to peripheral vasoconstriction and swelling, point-of-care sensors lose their benefit, and contemporary capillary samples become less accurate.

### 2.3 Significance of admission glucose level

Many studies have demonstrated that blood glucose disturbance is associated with increased mortality and morbidity. It has been estimated that each mmol/l rise in fasting blood glucose level is associated with a 33% increase in mortality in general medical ward patients. The risk for death increases in a U-shaped manner. The higher or lower the blood glucose level is outside of the normal range, the poorer seems to be the outcome. Changes in the blood glucose value and blood glucose variation may be even more associated with a poor outcome than mean blood glucose values. Some studies have even concluded that SIH is an independent marker of mortality. Admission hyperglycaemia during critical illness in patients without diabetes is more strongly associated with short-and long-term mortality and morbidity than in patients with diabetes, who are instead more at risk of long-term mortality. Patients without previously known diabetes and SIH have mortality rates that are three times higher than those of patients with previously diagnosed diabetes or normoglycaemic patients. Especially, a combination of hyperlactatemia together with hyperglycaemia seems to be a sign of poorer outcome. This is reasonable because metabolic alterations during critical illness lead metabolic pathways to shift mainly to glycolysis via increased energy demand, causing a disturbance in substrate availability and causing lactic acidosis production, a marker of severe disturbance in homeostasis.

### 2.4 Treatment of blood glucose disturbance during acute critical illness

#### 2.4.1 Treatment intervention with insulin

Giving insulin is thought to counteract SIH through several mechanisms. Insulin promotes excess glucose uptake into cells. Insulin takes part in lipogenesis; circulating free fatty acids are forced into small density lipoproteins by insulin and turned into triglycerides that are stored in adipose tissue, limiting the adverse effects of free fatty acids, such as arrhythmias. In addition to metabolic effects, insulin has other beneficial effects. It seems that insulin has cardio-protective, anti-
inflammatory, vasodilatory, antithrombotic, and endothelial protective properties as well 177–183.

The benefit of using insulin as a treatment is hindered by increased hypoglycaemia risk and increased variability in blood glucose level, especially in patients with diabetes who have pre-existing insulin resistance 162. Hence, a combination of glucose, potassium, and insulin is often used as a treatment of choice. The popularity of using a glucose-potassium-insulin (GIK) infusion is due to the observed beneficial results 181,184. In GIK, the insulin dosage is standardized compared with an insulin infusion, in which the rate of the insulin dosage is adjusted according to received glucose intake. Aside from the positive effects of GIK-infusion, glucose is thought to serve as an alternative, less energy-consuming fuel for ischaemic myocardial cells because free fatty acids are decreased by insulin 185. The risk of hypoglycaemia is also diminished with GIK-infusion. Potassium is added in the infusion to prevent hypokalaemia because insulin transports potassium into cells.

In the last two decades, researchers have debated about whether blood glucose disturbance should be treated or not, and if so, how and when should it be treated. The landmark study of van den Berghe, the Louven Study, showed that overall mortality was reduced by 34% in surgical ward patients with insulin intervention 33. These results initiated many multicentre studies. The Normoglycaemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study was the next trial that influenced treatment protocols 61. However, after the single centre study by van den Berghe in 2001, the Louven study, the positive mortality reduction results have not been repeated (Tables 1 and 2). This was also the case with the multicentre NICE-SUGAR study, in which an unexceptionally high prevalence of hypoglycaemia increased mortality risk 61. In trials such as Control of hyperglycaemia in paediatric intensive care (Chip), The Safe Paediatric Euglycaemia after Cardiac Surgery (SPECS), and Heart and lung failure-paediatric insulin titration trial (HALF-PINT), children were studied, and the results were similar to those of previous trials; insulin had little effect on mortality (Table 1).

In all SIH trials with ICU patients and in almost all SIH trials with acute coronary syndrome patients (Table 1 and 2), the study groups received glucose-insulin-potassium (GIK) infusion. Only HI-5 used insulin+glucose due to practical reasons 196. Depending on the trial, control groups either received saline placebo (saline) or standard treatment. The target blood glucose level and range of hypoglycaemia also varied depending on the trial (Tables 1 and 2). As a result, a consensus still cannot be achieved regarding the best treatment time, frequency, target, or parameters measured.
Table 1. Random controlled trials of treatment intervention in ICU patients with SIH.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Participants (N)</th>
<th>DM (%)</th>
<th>Time from ICU admission to treatment (hours)</th>
<th>Blood glucose measurement interval (hours)</th>
<th>Blood glucose target (mmol/l)</th>
<th>Hypoglycaemia risk (target definition)</th>
<th>Blood glucose sample</th>
<th>Mortality decreased (+), increased (-), no change (+/-)</th>
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<tbody>
<tr>
<td>Louven study 13</td>
<td>2001</td>
<td>Surgical (1548)</td>
<td>13</td>
<td>0-48</td>
<td>1-4</td>
<td>4.4-6.1 vs. 10.0-12.0</td>
<td>6-fold (&lt;2.2 mmol/l)</td>
<td>arterial</td>
<td>+</td>
</tr>
<tr>
<td>Hoedemaekers et al.</td>
<td>2005</td>
<td>Surgical (20)</td>
<td>0</td>
<td>0-1</td>
<td>1-8</td>
<td>4.4-6.1 vs &lt;11.1</td>
<td>not defined (&lt;2.2 mmol/l)</td>
<td>arterial</td>
<td>+/-</td>
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<tr>
<td>Louven Study 187</td>
<td>2006</td>
<td>Internal medicine (1200)</td>
<td>17</td>
<td>NA</td>
<td>1-4</td>
<td>5.9-6.8 vs. 10.0-12.0</td>
<td>6-fold (&lt;2.2 mmol/l)</td>
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<td>-</td>
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<td>Mitchell et al. 116</td>
<td>2006</td>
<td>Internal medicine (70)</td>
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<td>4-24</td>
<td>1-4</td>
<td>4.4-6.1 vs 10.0-11.1</td>
<td>5-fold (&lt;2.2 mmol/l)</td>
<td>arterial</td>
<td>+</td>
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<td>De la Rosa et al. 119</td>
<td>2008</td>
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<td>1-6</td>
<td>4.4-6.1 vs 10.0-11.1</td>
<td>6-fold (&lt;3.0 mmol/l)</td>
<td>arterial or capillary</td>
<td>-</td>
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<td>Arabi et al. 110</td>
<td>2008</td>
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<td>32</td>
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<td>1-4</td>
<td>4.4-6.1 vs 10.0-11.1</td>
<td>9-fold (&lt;2.2 mmol/l)</td>
<td>arterial or capillary</td>
<td>-</td>
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<td>Gluco-control study 141</td>
<td>2009</td>
<td>Mixed surgical and internal medicine (1101)</td>
<td>16</td>
<td>0-1</td>
<td>1-4</td>
<td>4.4-6.1 vs 7.8-10.0</td>
<td>3-fold (&lt;2.2 mmol/l)</td>
<td>arterial, venous, or capillary</td>
<td>-</td>
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<tr>
<td>NICE-SUGAR study 61</td>
<td>2009</td>
<td>Mixed surgical and internal medicine (6104)</td>
<td>20</td>
<td>0-24</td>
<td>NA</td>
<td>4.5-6.0 vs 7.8-10.0</td>
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<td>2011</td>
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<td>0-36</td>
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<td>-</td>
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<td>SPECS* 193</td>
<td>2012</td>
<td>Surgical (980)</td>
<td>0</td>
<td>0-1</td>
<td>continuous glucose monitoring</td>
<td>4.4-6.1 vs standard care</td>
<td>2-fold (&lt;3.0 mmol/l)</td>
<td>arterial</td>
<td>+/-</td>
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<td>CHIP* 104</td>
<td>2014</td>
<td>Mixed surgical and internal medicine (1569)</td>
<td>0</td>
<td>0-1</td>
<td>&lt;1</td>
<td>4.0-7.0 vs 10.0-12.0</td>
<td>6-fold (&lt;2.5 mmol/l)</td>
<td>arterial</td>
<td>+/-</td>
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<td>HALF-PINT* 105</td>
<td>2017</td>
<td>Internal medicine (1414)</td>
<td>0</td>
<td>NA</td>
<td>continuous glucose monitoring</td>
<td>4.4-6.1 vs 8.3-10.0</td>
<td>3-fold (not defined)</td>
<td>arterial or venous, (continuous glucometer)</td>
<td>+/-</td>
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*Trial with children. NICE-SUGAR=Normoglycaemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation trial; SPECS=The Safe Paediatric Euglycaemia after Cardiac Surgery; CHIP=Control of hyperglycaemia in paediatric intensive care; HALF-PINT=Heart and lung failure-paediatric insulin titration trial
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<th>Study</th>
<th>Year</th>
<th>n</th>
<th>DM (%)</th>
<th>Time from diagnosis of ACS to treatment (hours)</th>
<th>Blood glucose measurement frequency (hours)</th>
<th>Blood glucose target (mmol/l)</th>
<th>Hypoglycaemia risk (target definition)</th>
<th>Blood glucose sample</th>
<th>Mortality decreased (+), increased (-), not change (+/-)</th>
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<td>1995</td>
<td>620</td>
<td>100</td>
<td>0-24</td>
<td>1-2</td>
<td>9.6-15.4 vs. 11.7-15.7</td>
<td>15-fold (&lt;3.0 mmol/l)</td>
<td>venous</td>
<td>+</td>
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<td>GIPS 198</td>
<td>2003</td>
<td>940</td>
<td>11</td>
<td>0-24</td>
<td>1</td>
<td>7.0-11.0 vs local treatment protocol</td>
<td>not reported</td>
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<td>+/-</td>
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<tr>
<td>CREATE-ECLA trial</td>
<td>2005</td>
<td>20201</td>
<td>18</td>
<td>0-12</td>
<td>at 0, 6, and 24</td>
<td>9.0-10.4 vs 9.0-8.2</td>
<td>3-fold (&lt;3.0 mmol/l)</td>
<td>venous</td>
<td>+/-</td>
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<td>DIGAMI II study</td>
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<td>1253</td>
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<td>0-24</td>
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<td>7.0-10.0 vs local treatment protocol</td>
<td>9-12-fold (&lt;3.0 mmol/l)</td>
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<td>+/-</td>
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<td>GIPS-2 201</td>
<td>2006</td>
<td>889</td>
<td>10</td>
<td>0-6</td>
<td>1</td>
<td>6.0-10.0 vs local treatment protocol</td>
<td>not observed</td>
<td>venous</td>
<td>+/-</td>
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<td>HI-5 study</td>
<td>1996</td>
<td>240</td>
<td>48</td>
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<td>0, 6, and 12</td>
<td>12-fold (&lt;3.9 mmol/l)</td>
<td>arterial, venous, or capillary</td>
<td>arterial, venous, or capillary</td>
<td>-</td>
</tr>
</tbody>
</table>

SIH=stress-induced hyperglycaemia; ACS=acute coronary syndrome; DM=diabetes mellitus; DIGAMI=Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction trial; CREATE-ECLA=The Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment and Evaluation -Estudios Clínicos Latino América; GIPS=The Glucose Insulin Potassium Study; HI-5=Intensive Insulin Infusion In Infarction study; IMMEDIATE=Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency Care; OASIS-6=Organization for the Assessment of Strategies for Ischaemic Syndromes-6.

Thus far, one single RCT trial by Oksanen T et al. (2007) has compared intensive insulin treatment for strict (4.0-6.0 mmol/l) versus more moderate blood glucose target (6.0-8.0 mmol/l) in cardiac arrest patients. Informed consent from next of kin was obtained within 4 hours after ROSC, resulting in recruitment of 90 patients. Blood glucose was measured from arterial or venous samples. The results showed that insulin-infusion did not decrease mortality despite extensive evidence of SIH being associated with higher mortality.
As seen, studies have been very heterogeneous (Tables 1 and 2). The blood glucose target has varied from normoglycaemia (The first Louven Study) to mild permissive hyperglycaemia (CREATE-ECLA study) \(^3\)\(^{199}\). The study population has varied from mostly patients with diabetes (DIGAMI I and II studies) to all patient types (IMMEDIATE) \(^{203}\). The time and frequency of blood glucose measurement and the parameter studied (mean, time to target range, or variability, for instance) have varied between the studies.

Many studies have been prematurely stopped due to unacceptably high hypoglycaemia risk. These studies include CREATE-ECLA and GLUCOCONTROL-study \(^{191,199}\). The OASIS-6 GIK trial was stopped after the CREATE-ECLA results \(^{199,202}\). The DIGAMI II study was also prematurely stopped, not because of increased hypoglycaemia risk but instead due to too slow recruitment of the study population \(^{200}\). The GLUCOCONTROL-study showed a negative outcome and the CREATE-ECLA-study showed an indifferent outcome in mortality reduction \(^{191,199}\). However, it is worth mentioning that the GLUCOCONTROL, OASIS-6 GIK, and DIGAMI II studies were underpowered to detect the actual benefit of lowering glucose on mortality \(^{191,200,202}\).

Many studies have focused on critically ill patients treated in intensive care units or surgical wards and shown a lack of benefit due to high hypoglycaemia risk. Hence, very little is known about whether treatment should start in the very early phase, when blood glucose disturbance is first initiated, or when critical illness occurs. However, a smaller study by Nurmi et al. found a marked reduction in blood glucose in stroke patients when GIK-infusion was initiated in the prehospital surroundings revealing early insulin-intervention treatment to be feasible \(^{133}\). It seems that insulin treatment was started at the earliest time (by the EMS) in the IMMEDIATE study, with the exception of Nurmi et al., with a median time interval of 90 minutes \(^{203}\). However, in this IMMEDIATE trial, blood glucose target was not included in the study design \(^{203}\). Instead, the focus of the study was on decreasing circulating free fatty acids \(^{203}\). In other studies, initiation of treatment occurred later, up to 24-48 hours from onset of ACS, when pathophysiological processes had well developed. Therefore, treatment might not provide the best benefit (Tables 1 and 2). The difference in treatment timing may have greatly affected the differences in study results.

The difficulty of using insulin infusion with a known adverse risk of hypoglycaemia has concerned cardiologists in particular \(^{203}\). Thus, studies with ACS (DIGAMI I and II, CREATE-ECLA, and IMMEDIATE) have primarily used GIK-infusion \(^{197,199,200,203}\). Although GIK-infusion has been found to be beneficial in some studies \(^{181,184,206}\), in most studies, the results have been indifferent or harmful (Tables 1 and
2) \[^{170,178,207}\]. Giving intravenous glucose to critically ill patients with SIH increased mortality \[^{207}\]. Hence, the glucose in GIK-infusion may have influenced the negative or indifferent results of recent trials. It seems that that insulin infusion should be the preferred intervention method with tight blood glucose control compared with GIK-infusion \[^{13,187,208}\].

### 2.4.2 Treatment intervention with GLP-1 analogues

Some small studies of native GLP-1 infusion and GLP-1 analogues with exenatide have gained positive results for treatment of SIH. GLP-1 analogues increase endogenous insulin and inhibit glucagon production in a glucose-dependent manner, thereby attenuating glycaemic variability without causing hypoglycaemia (Table 3) \[^{209–211}\]. GLP-1 analogues seem to carry cardio-protective and neuroprotective benefits \[^{212,213}\]. This makes them possibly an ideal treatment medication for SIH. Hence, GLP-1 analogues have been studied for a potential alternative treatment for insulin. Current studies have primarily been pilot studies. Few RCTs exist that have examined myocardial infarction patients, and only one has evaluated cardiac arrest patients (Table 3). All of these RCTs show that GLP-1 seems to have good potential as a treatment option for critically ill patients with SIH. GLP-1 agonists seem to improve left ventricular function, decrease infarct size, and preserve microvascular endothelial function \[^{214–216}\]. The hindrance is that there is not enough information concerning how this novel medication acts pharmacokinetically and pharmacodynamically in critically ill patients who can at the same time suffer from renal or liver failure. Further RCTs needs to be conducted to generalize these results. Current studies have been too small to make any assumptions of mortality. Larger, multicentre studies need to be conducted to study mortality benefit. A study comparing insulin and GLP-1 treatment for SIH should also be conducted.
Table 3. Random controlled trials studies of treatment intervention with GLP-1 analogues for SIH patients in the ICU.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Hypoglycaemia risk</th>
<th>Intervention (endogenous GLP-1 infusion=1, GLP-1-analogue infusion=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sokos et al. 217</td>
<td>2007</td>
<td>20</td>
<td>CABG surgery patients</td>
<td>GLP-1 vs placebo</td>
<td>Significant blood glucose reduction in peri-and postoperative glucose values, fewer insulin and antiarrhythmic agents required</td>
<td>1 incident in GLP-1 group and 2 receiving placebo</td>
<td>1</td>
</tr>
<tr>
<td>Deane et al. 218</td>
<td>2009</td>
<td>25</td>
<td>mechanically ventilated ICU patients</td>
<td>GLP-1 vs placebo</td>
<td>GLP-1 lowered postprandial hyperglycaemia in critically ill patients</td>
<td>none</td>
<td>1</td>
</tr>
<tr>
<td>Deane et al. 219</td>
<td>2013</td>
<td>7</td>
<td>mechanically ventilated patients with diabetes</td>
<td>GLP-1 2 times+ placebo for a time interval 4 h 30 min</td>
<td>GLP-1 attenuated glycaemic response in the critically ill patients</td>
<td>none</td>
<td>1</td>
</tr>
<tr>
<td>Galiatsatos et al. 220</td>
<td>2014</td>
<td>18</td>
<td>surgical or burn patients</td>
<td>GLP-1 vs placebo</td>
<td>Less exogenous insulin required with GLP-1, less glucose variability, and significant increase in cardiac function</td>
<td>none</td>
<td>1</td>
</tr>
<tr>
<td>Wiberg et al. 220</td>
<td>2016</td>
<td>120</td>
<td>unconscious cardiac arrest patients</td>
<td>GLP-1 vs placebo</td>
<td>no neurological improvement, but administration of GLP-1 proved safe</td>
<td>3 incidents with GLP-1 and one receiving placebo</td>
<td>2</td>
</tr>
</tbody>
</table>

CABG=Coronary Artery Bypass Graft; GLP-1=glucagon-like-peptide-1

2.5 “Track and trigger” systems

Different “track and trigger” systems, also known as early warning scores, have become popular in the hospital and prehospital surroundings to help in discriminating the risk of patient deterioration. “Track and trigger” systems are processes that rely on periodic measurements that observe certain specified parameters (track) and certain thresholds (trigger). They are used as a warning score for risk determination. “Track and trigger” systems rely on commonly measured parameters. Of these the National Early Warning Score (NEWS) was developed by Royal College of Physicians in UK in 2012 221. Thus far, it has been shown to be the best discriminating screening tool 222. A high NEWS has been found to be strongly associated with increased mortality and ICU admission 223. Additionally, in prehospital surroundings, especially in trauma cases, patients
Blood glucose disturbance in patients encountered by the emergency medical service scoring in the high NEWS category are predicted to have higher mortality within one day compared with those scoring in the moderate or low NEWS categories. However, it is noteworthy that NEWS can overestimate the medical risk of a patient because it is affected by chronically abnormal physiological parameters seen in chronic diseases.

Because blood glucose disturbance has been demonstrated to have a strong association with poorer outcome, blood glucose has been investigated in some “track and trigger” systems for better discrimination of risk of poorer outcome (Table 4). Abbott et al. used point-of-care testing and NEWS, but blood glucose was not weighed or added as an additional parameter to NEWS. In the Prince of Wales Emergency Department Score (PEDS) “track and trigger” system, blood glucose was used as a parameter with positive benefit, but otherwise, this “track and trigger system was not comparable to NEWS.

Table 4. Studies of “track and trigger” systems that included blood glucose.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>N</th>
<th>Participants</th>
<th>Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattermole et al. (2009)</td>
<td>330</td>
<td>Emergency department patients</td>
<td>PEDS vs PEDS+glucose</td>
<td>PEDS+glucose may help in predicting the likelihood of early ICU admission.</td>
</tr>
<tr>
<td>Glassberg et al. (2013)</td>
<td>706</td>
<td>Prehospital trauma patients</td>
<td>ISS vs ISS+glucose</td>
<td>ISS+glucose added benefit in severely wounded</td>
</tr>
<tr>
<td>Timotéo et al. (2014)</td>
<td>2099</td>
<td>ACS</td>
<td>GRACE vs GRACE+glucose</td>
<td>GRACE+glucose added modest benefit</td>
</tr>
<tr>
<td>van Toorenburg et al. (2018)</td>
<td>2055</td>
<td>ACS</td>
<td>GRACE vs GRACE+glucose and additional biomarkers</td>
<td>GRACE+ glucose and additional biomarkers* improved score risk stratification significantly.</td>
</tr>
<tr>
<td>Abbott et al. (2018)</td>
<td>322</td>
<td>Medical ward patients</td>
<td>NEWS vs NEWS+lactate, glucose, and base-excess</td>
<td>Blood glucose was not associated with increased mortality or ICU admission</td>
</tr>
<tr>
<td>McCall et al. (2018)</td>
<td>5575</td>
<td>Stroke patients</td>
<td>SOAR vs SOAR+glucose</td>
<td>SOAR+glucose added only modest benefit</td>
</tr>
</tbody>
</table>

ACS=Acute Coronary Syndrome; ISS=Injury Severity Score; GRACE=Global Registry of Acute Coronary Events; SOAR=Oxford community Stroke Project classification, age, and prestroke modified Ranking
In two studies, blood glucose was added into Global Registry of Acute Coronary Events (GRACE) and in one study to Oxford community Stroke Project classification, age, and prestroke modified Rankin (SOAR)\textsuperscript{231–233}. In the first study of GRACE and with SOAR, blood glucose was studied as a single additional biomarker\textsuperscript{231–233}. In the later GRACE study, multiple biomarkers were studied in combination with blood glucose\textsuperscript{231,232}. All of these studies found that blood glucose added modest or no benefit in the scoring system.

These modest findings from previous studies have possibly caused a lack of interest in further studies on adding blood glucose into a “track and trigger” system. However, in these previously studied “track and trigger” systems blood glucose was in some studies categorised, although the categories were not weighted and hypoglycaemia was not usually included. When studying blood glucose without categorization, most patients will present with normoglycaemia or moderate hyperglycaemia, which will give an indifferent result because those patients will likely not have SIH or spontaneous hypoglycaemia, a phenomenon associated with a poorer outcome.

Even an optimal “track and trigger” system should be used only as an aid for clinical decision making. It should not replace human decision making but rather be used in combination to guide better patient care.
3 STUDY QUESTIONS

The aim of the present study was to describe blood glucose disturbance during acute illness encountered by the EMS. In more detail, the aims were as follows:

1. How is blood glucose disturbance associated with critical illness?
2. How commonly is hypoglycaemia without diabetes encountered by EMS?
3. What are the initial pathophysiological mechanisms of SIH in OHCA?
4. Does blood glucose improve better discrimination of risk of death when added to national early warning score (NEWS)?
4 MATERIALS AND METHODS

4.1 Study design

The study consisted of four parts: one observational prospective (III) study and three register-based retrospective (I, II, and IV) studies (Table 5).

Table 5. Characteristics of study design.

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants (N)</th>
<th>Study setting</th>
<th>Exposure</th>
<th>Comparison</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>152 patients with ST-elevation myocardial infarction</td>
<td>Helsinki EMS</td>
<td>Change in blood glucose from prehospital contact to ED admission</td>
<td>Change in blood glucose or stable blood glucose from prehospital contact to ED admission</td>
<td>Death at 30 days and at three years</td>
</tr>
<tr>
<td>II</td>
<td>3856 patients without diabetes</td>
<td>EMS of HUCH</td>
<td>Hypoglycaemia not related to diabetes</td>
<td>None</td>
<td>Mortality at 24 hours, 30 days and one year</td>
</tr>
<tr>
<td>III</td>
<td>28 patients successfully resuscitated from OHCA regardless of initial rhythm and a written informed consent from next of kin</td>
<td>Two physician-staffed units</td>
<td>Prehospital levels and early changes in circulating insulin, glucagon, GLP-1, IL-6, cortisol, and B-HbA1c</td>
<td>None</td>
<td>Change in blood glucose from point of ROSC to ED admission</td>
</tr>
<tr>
<td>IV</td>
<td>27141 patient cases with all NEWS parameters and a blood glucose measurement</td>
<td>EMS of hospital district of Helsinki and Uusimaa</td>
<td>NEWS with glucose as an additional parameter</td>
<td>Standard NEWS</td>
<td>Death at 24 hours and at 30 days</td>
</tr>
</tbody>
</table>

ED=Emergency Department; EMS=Emergency Medical Service; HUCH=Helsinki University Central Hospital; HUS=Hospital District of Helsinki and Uusimaa; NEWS=National Early Warning Score

4.2 Study setting

The district of Helsinki and Uusimaa is covered by one single EMS system. This is a public three-tiered system with basic life support, advanced life care, and two physician-staffed units (a HEMS and a ground unit). The district of Helsinki and Uusimaa covers the entire Helsinki metropolitan area with a population of 1.6 million inhabitants (Helsinki, Espoo, Vantaa, Kauniainen, Kirkkonummi, and Kerava), depending on when the electronic EMS database (MerlotMedi®, CGI,
Blood glucose disturbance in patients encountered by the emergency medical service (Suomi oy, Helsinki, Finland) was implemented. The Helsinki University Central Hospital area covers the more inner urban district area with a population of 1 million inhabitants (Helsinki, Espoo, Vantaa, and Kauniainen). The Helsinki city area covers a population of 575,000 inhabitants in the city of Helsinki. Patients are typically transported to six receiving public hospitals in the Helsinki metropolitan area. Patients may also be treated and left on the scene if hospital treatment is not needed. In the prospective study design, recruitment was performed only during office hours, when essential laboratory facilities were available (III).

4.3 Participants

The study retrospectively gathered data from 469 ST-elevation myocardial infarction patients manually from the EMS patient records, which was then combined with hospital record laboratory data (I). Of these, 32% (n=152) had prehospital and hospital admission plasma glucose values measured, which were included in the final analysis (I). Data of 13135 hypoglycaemic patient cases were collected from electronic EMS database from January 2009 to December 2015 from Helsinki University Central Hospital area (II). These data were further divided into patient cases with diabetes and without diabetes (II). For categorization, the database of Social Insurance Institution of Finland was used to find diabetes medication (II). Data of 3856 patients without diabetes were used for final analysis, and data of 250 patients without diabetes and severe hypoglycaemia were used as a subgroup (II). From January 2014 to July 2015, 30 adult patients with successfully resuscitated out-of-hospital cardiac arrest (OHCA) regardless of initial rhythm were recruited (III). Due to errors in laboratory sampling, two cases needed to be excluded (III). This resulted in inclusion of 28 cases for final analysis (III). Data of 27141 adult patient cases with fully recorded NEWS parameters and a blood glucose measurement were collected from the electronic EMS database from August 2008 to December 2015 (IV). Survival of the patients was defined by the Statistics of Finland registry data office (II and IV). Prediabetes was categorized as having HbA1c ≥6.5% within the past three months of the incident and a random blood glucose measurement ≥11.1 mmol/l (I and III) or determined by a time interval of three years from the EMS incident to purchase of diabetes medication later than hospital admission (II). In patient cases included in the study evaluating addition of blood glucose as a parameter in NEWS, HbA1c was not recorded and prediabetes could not be defined (IV). Prediabetes was found in 3-11% of patients depending on the study data. The inclusion criteria were over 18 years of age (I, III, and IV), a blood glucose measurement (I-IV), a diagnostic ST-elevation myocardial infarction with typical onset of pain and EKG changes (I), a successfully resuscitated OHCA patient from any initial arrhythmia (III), and all NEWS parameters were recorded.
(IV). Exclusion criteria were age under 18 years (I-III), pregnancy (I-IV), invalid personal identity number (I-IV), missing or invalid data (I-IV), and lack of receipt of informed written consent from next-of-kin (III), or if patient safety would have been compromised (III).

### 4.4 Prehospital assessment and study samples

Vital parameters were recorded in the prehospital surroundings with a monitor-defibrillator (Zoll M series and X series (Zoll Medical Corporation Inc., 269 Mill Rd, Chelmsford, MA, USA) or LifePak 12 and 15 (Physio-Control Inc., 11811 Willows Rd NE, Redmond, WA, USA)). Respiration rate, level of consciousness, and temperature were recorded manually by the EMS personnel on scene. Blood glucose was measured according to the local EMS protocol, which included patients who experienced a lowered level of consciousness, sudden deterioration of overall wellness from an unknown cause, disorientation, seizure, hypothermia, or a diabetic patient who was feeling unwell (I-IV). EMS personnel primarily measured plasma glucose from capillary finger-tip samples using calibrated plasma analysis devices (Optimum Xceed® glucometer and MediSense Optimum electrodes®, Abbott Laboratories, Alameda, CA) (I-IV). Occasionally, blood glucose samples were taken from venous or arterial blood. No records were kept regarding the blood source for the blood glucose measurement.

### 4.5 Analytical methods for study samples

In the prospective study of OHCA patients, first plasma samples were taken in prehospital surroundings and second plasma samples were obtained at hospital admission (III). In the prehospital surroundings, plasma samples for glucose, insulin, glucagon, and GLP-1 measurements were first taken from venous or arterial blood. Glucose and insulin were drawn into citrate-fluoride and serum-gel tubes. Plasma samples for glucagon and GLP-1 measurements were drawn in protease, esterase, and DPP-IV inhibitor-containing PD P800 (Becton, Dickson and Company, NJ, USA) tubes. These tubes were covered in ice packs and delivered to the hospital with the patient. At hospital admission, the prehospital glucose, insulin, and glucagon plasma samples were taken to the hospital laboratory for immediate analysis. Only plasma-GLP-1 samples were frozen at -70°C for later separate analysis via Enzyme Linked Immunosorbent Assay (ELISA). At hospital admission, a second set of plasma samples were taken from the study patients. Glucose, insulin, glucagon, GLP-1, IL-6, cortisol, and HbA1c plasma samples were drawn from arterial or venous blood. Glucose and insulin were again drawn into
citrate-fluoride and serum-gel tubes. Plasma-glucagon and plasma-GLP-1 were
drawn into protease, esterase and DPP-IV inhibitor-containing tubes. Plasma-IL-6
was drawn into a heparin-containing tube, plasma-cortisol into serum-gel tubes,
and plasma-HbA1c into K2-EDTA-containing tubes. These hospital admission
plasma samples were routinely analysed immediately in the hospital laboratory.

4.6 Ethical approval

The prospective study protocol was approved by the Ethics Committee of Helsinki
University Central Hospital (357/13/03/02/2012), and the study protocol was
registered at clinicaltrials.gov (NCT01968148) (III). The retrospective studies were
registry-based (I, II, and IV). According to Finnish legislation, no ethical approval
was needed for these studies. All studies were conducted according to the Finnish
Medical Research Act and conformed with the principles of the Declaration of
Helsinki.

4.7 Statistical methods

Continuous variables are presented as the mean and standard deviation (mean±SD)
(I) or median and interquartile range (median, IQR) (I-IV). Categorical variables
are presented as percentages with 95% confidence intervals (I-IV). Continuous
variables were compared using Mann-Whitney test or an unpaired t-test and
Wilcoxon matched-pairs signed rank test when appropriate (I-IV). Comparisons of
categorical variables are performed with a chi-square test or Fischer exact test when
appropriate. Spearman’s correlation coefficient was used to analyse associations
between continuous variables (III). Univariate and multivariate analyses were used
to calculate odds ratios (II and IV). Kaplan-Mayer curves were plotted for survival
analysis and a log-rank test was used to study correlation (II). Comparison of
two models was achieved with area under the receiver operating curve (AUROC),
likelihood ratio tests (LRTs), and calibration with a Hosmer-Lemeshow test (IV).
Reclassification was performed using the continuous net reclassification index
(cNRI) and integrated discrimination improvement (IDI) (IV).

Reclassification is a method used for testing disease risk with variable(s) known to
be related to risk. cNRI is used for studying how well the net portion of subjects are
reclassified correctly using the new model compared with the older one. The cNRI
can receive values from -2 to 2 because it is the sum of the proportion of event
and non-event observations that were correctly reclassified. A value of 2 indicates
that the new model classified 100% of the events and non-events better than the
old model. IDI is the mean change in predicting risk for events minus the mean risk change of non-events between the new and old model. The IDI model tells us how much on average the new model improves the risk prediction. The IDI can also receive values from -2 to 2. However, a value of 2 would mean that the old model incorrectly predicted all non-events to have 100% risk of the event and the events to all have 0% risk of event. At the same time, the new model would predict 100% risk of all the events and 0% risk for all the non-events. Statistical analyses were carried out with GraphPad Prism 5.0 Mac OS X, GraphPad Prism 6.0 Mac OS X, GraphPad Prism 7.0 Mac OS X, and R (version 3.4.4.) using the ggplot2, cowplot, plotROC, pROC, and ResourceSelection packages 234–238.
5 RESULTS

5.1 Characteristics (Studies I-IV)

5.1.1 Study I

During the study period, 152 of 469 patients had valid prehospital and hospital admission glucose measurements, which were included in the final analysis (Table 6). Male patients dominated (70%), with a median age of 61 years. Diabetes was prevalent in 25% (38/152) and prediabetes in 8% (12/152) of patients. Anterior myocardial infarction was common (47%). Of note, only 24% of patients had previously known coronary heart disease.

5.1.2 Study II

Among 13135 hypoglycaemic cases, 3856 cases without diabetes from HUCH were included in the final analysis. Of those, 6% (250/3856) of the patients experienced severe hypoglycaemia (≤3.0 mmol/l) and 2% (70/3856) had prediabetes. The incidence of hypoglycaemia without diabetes encountered by the EMS was 1082 (CI95% 1019-1148) per 100,000 inhabitants. In the study, 65% of the patients were male, with a median age of 57 years.

5.1.3 Study III

For the study, 30 adult patients were recruited with OHCA and a subsequent successful cardiopulmonary resuscitation. Two of the patients had errors in blood glucose sampling and hence were excluded. As a result, data of 28 patients reached final analysis. Of those, 29% had previously known diabetes (all type 2), and of those patients without diabetes 11% (3/28) had prediabetes. Patients without diabetes had a median age of 70 years (range 41-84), and patients with diabetes had a median age of 73 years (range 55-85). Coronary heart disease and hypertension were more common in patients with diabetes than in those without diabetes. All patients, except two, were hyperglycaemic in the prehospital surroundings and remained hyperglycaemic at hospital admission. The two hypoglycaemic cases became hyperglycaemic at hospital admission. Overall, the blood glucose level decreased in 22 patients and increased in 6 patients. The hospital has a specified insulin treatment protocol for hyperglycaemia. However, there was insufficient data in hospital patient records to make any valid conclusion of administered insulin intervention during the hospital stay.
5.1.4 Study IV

EMS received 750694 calls in the district of Helsinki and Uusimaa in 2008-2015. Of those, 27141 had all NEWS parameters recorded and a valid blood glucose measurement. The median age of a patient was 69 years (range 18-104). Half of the patients were male, who more often experienced severe hypoglycaemia (≤3.0 mmol/l) [1.2% (CI95% 1.0-1.4)] compared with female patients [0.7% (CI95% 0.6-0.8), p<0.001]. Severe hypoglycaemia was more prevalent in younger patients with a median age of 62 years (range 18-65), and stress-induced hyperglycaemia was more common in more elder patients with a median age of 74 years (range 65-96).

Table 6. Patient characteristics in Studies I-IV. The data are presented as the median and interquartile range (IQR) except for sex, hypertension, coronary artery disease and diabetes, which are presented as percentages with 95% confidence intervals. Age is presented as the median and range.
5.2 Incidence and prevalence of blood glucose disturbance encountered in emergency medical service

Random blood glucose disturbance was common in patients both with and without diabetes (Figure 9). Most STEMI-patients were found to be hyperglycaemic in the prehospital surroundings (I). Of those, two thirds of the study patients had 7.0 mmol/l or above prehospital blood glucose values and one fifth of the patient’s had 11.1 mmol/l or above blood glucose values (I). Only five cases encountered by EMS had hypoglycaemia (≤4.0 mmol/l) (I). OHCA patients were almost all hyperglycaemic in the prehospital surroundings at the time of blood sampling and stayed hyperglycaemic at hospital admission blood sampling [96 min (IQR 85-119)] (III). Of those, 86% had a blood glucose of 7.0 mmol/l or above and 61% had a value of 11.1 mmol/l or above; two cases had hypoglycaemic values in the prehospital setting (2.6 mmol/l and 3.6 mmol/l) (III). Among patients with all NEWS parameters and blood glucose measurement, two out of three had hyperglycaemia (IV). Of those, 56% had a blood glucose value of 7.0 mmol/l or above, and 14% had a value of 11.1 mmol/l or above; hypoglycaemia (≤4.0 mmol/l) was encountered in 3% of the cases (IV). Of those, 1% had severe hypoglycaemia (≤3.0 mmol/l) (IV). Overall, 76-93% of patient cases had hyperglycaemia (I-IV), 3-7% had hypoglycaemia (I, III, and IV), and among those, 42-75% (I-IV) were without diabetes and of those, prediabetes was found in 2-11% (I-III).

![Hyperglycaemia, normoglycaemia, and hypoglycaemia encountered in Studies I, III, and IV. The data are presented as percentages (%).](image)

Study I. STEMI patients from Helsinki City area in 2006-2010.
Study III. Successfully resuscitated OHCA patients from HUCH in 2014-2015.
Study IV. Patients cases with all NEWS parameters and a blood glucose measurement in district of Helsinki and Uusimaa recorded in 2008-2015.

Figure 9. Hyperglycaemia, normoglycaemia, and hypoglycaemia encountered in Studies I, III, and IV. The data are presented as percentages (%).

STEMI=ST-elevation myocardial infarction; HUCH=Helsinki University Central Hospital; OHCA=Out-of-hospital cardiac arrest; NEWS= National Early Warning Score.
5.3 Very early mechanisms of blood glucose disturbance

The prospective study of OHCA patients focused on the very early pathophysiological mechanisms of SIH (III). Marked interindividual variation was found within biomarkers, and no correlation between change in blood glucose and change in insulin ($r=0.30$, $p=0.13$), change in glucagon ($r=0.29$, $p=0.17$), change in GLP-1 ($r=0.32$, $p=0.15$), hospital admission IL-6 ($r=-0.07$, $p=0.75$), hospital admission cortisol ($r=0.13$, $p=0.52$) or hospital admission HbA1c level ($r=0.34$, $p=0.08$) was observed. Fifteen patients (54%) did not receive exogenous epinephrine (III). When exogenous epinephrine was not administered, a change in blood glucose was correlated with a change in insulin and a change in glucagon ($r=0.59$, $p=0.04$ and $r=0.65$, $p=0.05$ respectively). Table 7 shows the concentrations of biomarkers obtained after immediate resuscitation after ROSC and at hospital admission in all studied patients. Insulin and glucagon levels were near fasting levels (reference: insulin 10-20 mU/l and glucagon <209 ng/l \(^{29}\)). At the same time, the GLP-1-level increased 2- to 8-fold (reference: 1-2 ng/ml \(^{67,68}\)) along with an elevation in IL-6. Insulin resistance, calculated by the HOMA-IR index, was observed, but in a U-shaped manner, with half of the cases experiencing increasing and half of the cases experiencing decreasing resistance at hospital admission, although the insulin level was low. We also studied hospital admission IL-6, cortisol, and HbA1c-levels. Different interindividual differences were widely present in the IL-6 level (range 6-899 ng/l). With an exception of few outliers, IL-6 was not increased markedly, presenting with a median value of 32 ng/l (IQR 22-63).
Table 7. Studied biomarkers in Study III. The data is represented as median (IQR).

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>All</th>
<th>Without epinephrine</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>28</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Insulin (mU/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>prehospital</td>
<td>10.2 (25.4-25.7)</td>
<td>8.2 (5.1-8.7)</td>
<td>0.7137</td>
</tr>
<tr>
<td>hospital admission</td>
<td>9.8 (2.4-24.4)</td>
<td>6.6 (2.4-24.9)</td>
<td>0.7317</td>
</tr>
<tr>
<td>change</td>
<td>0.3 ((-4.3)-8.7)</td>
<td>0.3 ((-3.9)-10.7)</td>
<td>0.9829</td>
</tr>
<tr>
<td>Glucagon (ng/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>prehospital</td>
<td>141 (106-243)</td>
<td>127 (105-171)</td>
<td>0.6781</td>
</tr>
<tr>
<td>hospital admission</td>
<td>127 (65-170)</td>
<td>126 (65-129)</td>
<td>0.6944</td>
</tr>
<tr>
<td>change</td>
<td>-32 ((-55)-23)</td>
<td>-42 ((-83)-25)</td>
<td>0.4843</td>
</tr>
<tr>
<td>GLP-1 (mg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>prehospital</td>
<td>6.3 (5.1-9.0)</td>
<td>6.4 (6.0-8.8)</td>
<td>0.7566</td>
</tr>
<tr>
<td>hospital admission</td>
<td>5.8 (4.9-8.7)</td>
<td>6.0 (5.3-8.1)</td>
<td>0.8224</td>
</tr>
<tr>
<td>change</td>
<td>-0.2 ((-0.1)-0.2)</td>
<td>-0.3 ((-1.5)-0.05)</td>
<td>0.4861</td>
</tr>
<tr>
<td>IL-6 (ng/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hospital admission</td>
<td>32 (22-63)</td>
<td>27 (16-57)</td>
<td>0.3966</td>
</tr>
<tr>
<td>cortisol (nmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hospital admission</td>
<td>623 (449-748)</td>
<td>518 (342-697)</td>
<td>0.2423</td>
</tr>
<tr>
<td>B-GHbA1c (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hospital admission</td>
<td>5.8 (5.5-6.4)</td>
<td>6.0 (5.5-6.6)</td>
<td>0.4016</td>
</tr>
</tbody>
</table>

5.4 Usability of blood glucose as a marker of outcome

We found that adding blood glucose to NEWS improved identification for risk of death in the prehospital setting. In the new NEWS model (NEWSgluc), stress-induced hyperglycaemia (≥11.1 mmol/l) received 1 point, normoglycaemia 0 points, and severe hypoglycaemia (≤3.0 mmol/l) 3 points. The usability of this new NEWSgluc model was profoundly analysed to minimize bias. A multivariable regression model with blood glucose as an additional parameter revealed that hyperglycaemia had a moderate [24 hours risk of mortality: OR 1.54, (1.11-2.12) and 30 days risk of mortality: OR 1.41, (1.20-1.66)] and hypoglycaemia had a strong [(24 hours risk of mortality: OR 5.46, (2.87-9.64) and 30 days risk of mortality: OR 2.33, (1.47-3.52)] association with short- and long-term risk of mortality. This meant that with hypoglycaemia only the categories “heart rate<40/min”, “breathing >25/min”, and “level of unconsciousness parameter” discriminated a higher 24-hour risk of death. Hyperglycaemia discriminated more moderately risk of death at 24 hours and at 30 days. Likelihood ratio tests (LRTs) were both p<0.001. Although areas under the receiver operating curve (AUROC) were similar for NEWSgluc (AUROC 0.870) and NEWS (AUROC 0.864), the reclassification tests, cNRI and IDI, showed overall improved classification of survivors and non-survivors at
24 hours and at 30 days. cNRI was at 24 hours risk of mortality 0.413, (CI95% 0.281-0.545) and at 30 days risk of mortality 0.254, (CI95% 0.197-0.311), p<0.001. IDI was significant at 30 days (0.002, CI95% 0.001-0.003, p<0.001). Risk per score point and calibration of the model further improved the discrimination capability of the NEWSglue model for risk of death at 24-hours and at 30-days.
6 DISCUSSION

6.1 Summary of the main findings

In the prehospital surroundings, hyperglycaemia was encountered in 76-93% and hypoglycaemia in 3-7% of patients, depending on the gathered data (I, III, and IV). SIH and hypoglycaemia during critical illness in patients with or without diabetes were associated with increased mortality (I, II and IV). In the EMS, the observed hypoglycaemic episodes without diabetes seemed to be caused by a known factor (alcohol abuse, hypothermia, malnutrition or intoxication) that was not related to critical illness (II). These hypoglycaemic episodes without presentation of critical illness were associated with better outcome than when renal failure, liver failure, cancer, or congestive heart was present (II). In the latter, spontaneous hypoglycaemia was more likely present (II). Very early physiological mechanisms of blood glucose disturbance seemed to differ from the physiological mechanisms of SIH found in hospital surroundings (III). It is possible that it may be due to the global ischaemic insult from OHCA or otherwise different initial mechanisms as both insulin and glucagon levels were low in contrast with the elevated levels seen in SIH. Blood glucose disturbance seems to be a good additional parameter to add to the National Early Warning Score (NEWS) for better discrimination of patients at risk of death. This was confirmed by studying the logistic regression model and by using calibration methods, risk per score point, and reclassification methods.

6.2 Originality of the study

Hyperglycaemia was common during critical illness (I, III, and IV), and actual spontaneous hypoglycaemia was rare (I-IV) due to the body’s strong defence mechanisms against hypoglycaemia. This association is well supported by previous literature. Previous studies have primarily been performed in hospital surroundings and showed physiological changes after two or even 24 hours. We focused on the very early phase, seen by the EMS, providing insight into the earlier moments of blood glucose disturbance development. Insulin and glucagon levels were found to be low in contrast with typical characteristics of SIH (insulin resistance and elevated counterregulatory hormone levels) (III). The endogenous GLP-1 level was also increased 2-8-fold (III). All biomarkers (insulin, glucagon, GLP-1, IL-6, cortisol, and HbA1c) had interindividual variation, and were not associated with changes in blood glucose from the prehospital sample to the hospital admission sample (III). However, the conducted study design was difficult
due to laboratory facilities being open only on the weekdays between the hours of 8.00 am and 4 p.m. and because informed verbal and written consent was needed from the next of kin in the prehospital surroundings to include patients, resulting in a small amount of gathered data. Very few studies with a similar study design have been found in the previous literature. Because no causal relationship could be established, the study results cannot be generalized. Hence, the results are considered explorative in nature. The possible reasons for low insulin and glucagon levels is discussed in Figure 10.

**Figure 10.** Possible mechanisms that may explain low insulin and glucagon levels in the initial phase of blood glucose homeostasis disturbance. Elevated epinephrine level due to sympathetic nervous system axis, changes in substrate availability and energy homeostasis, low insulin level, and downregulation of CNS-GLP-1 secretion potentiated by cortisol secretion all enhance directly or indirectly glucagon secretion, the key contributor for development of SIH. IL-6=interleukin 6; Central GLP-1=glucagon-like-peptide-1 secreted from the brain.

In the first seconds, minutes, and hours after encountering acute critical illness, blood glucose disturbance begins to develop. Glucose uptake is enhanced by TNF-alpha and IL-1 via GLUT-1, which increases non-insulin-mediated glucose uptake by the cells, especially in the central nervous system, spleen, liver, kidney, skin, lung, and ileum. GLP-1, secreted from the intestine, is not able to cross the blood-brain barrier. CNS GLP-1 is instead secreted in the brain and leads to activation of the sympathetic nervous system and modulation of the actions of the hypothalamic-pituitary-axis. CNS GLP-1 seems to act by balancing...
the peak of blood glucose disturbance. In addition to these effects, CNS GLP-1 seems to take part in behavioural changes by increasing anxiety. This may help the patient in gaining better situational awareness even before actual critical illness has occurred.

In the very initial phase, energy expenditure may be reduced resulting in decreased insulin secretion. Substrate availability may still be sufficient, which may directly hinder glucagon secretion. Highly increased epinephrine secretion is known to strongly inhibit insulin secretion and enhance glucagon secretion, although CNS GLP-1 and intestinal GLP-1 act oppositely by increasing insulin secretion and inhibiting glucagon secretion. Also a decreasing blood glucose level (0.4-0.8 mmol/l) due to the increased glucose influx into cells may decrease insulin secretion. Hence, in the early phase of blood glucose disturbance, a relatively slow rise in insulin and glucagon level may be seen.

Shortly after the initial phase, the brain decreases CNS GLP-1 secretion directly, which is further enhanced by cortisol secretion after a few hours. Hence, the inhibitory effect of CNS-GLP-1 on glucagon is decreased leading to a further rise in glucagon level. It seems to be essential that CNS-GLP-1 is secreted in a pulsatile manner so that the body is not sensitized to stress but instead is kept alert for possible new stressors. Because glucocorticoids act slower, the observed action is fully seen after 1-2 hours of the occurrence of stress and disturbance in body homeostasis. Increasing glucagon level, relative insulin deficiency along with activation of the cortisol feedback mechanism affecting CNS-GLP-1 may be the turning point for development of the more commonly known SIH. In support of this hypothesis, cortisol levels were still in the normal range at hospital admission in OHCA patients, with a median value of 623 nmol/l, (IQR 449-748) (III). Thus far it seems that no study on the association between CNS GLP-1 secreted from the brain and blood glucose homeostasis disturbance during acute critical illness has been conducted in the prehospital surroundings. It is possible that CNS GLP-1 actions may differ from the known actions of intestinal GLP-1. Unfortunately, neither catecholamine nor growth hormone levels were studied (III). These biomarkers would have given further insight into the current findings.

Variability in blood glucose disturbance may possibly be as a sign of the body balancing between the very early physiological mechanisms discussed here and typical SIH development, depending on the different feedback mechanisms in action. To support this notion, a study by Vitek et al. found that the mean value possibly should not be studied, but instead, we should focus on variability during the very early phase of blood glucose disturbance.
When added to NEWS, early blood glucose homeostasis disturbance seemed to better discriminate patients at risk of death compared with when blood glucose was not included in NEWS. Although rare, spontaneous hypoglycaemia during critical illness seemed especially to be a sign of increased risk of death. Blood glucose disturbance seemed to develop early in the prehospital surroundings, and it seems to be related to overall disturbance in body homeostasis and not an independent marker of the cause of severe illness. To support this, a higher NEWS with glucose as an additional parameter was associated with higher mortality risk compared with a lower NEWS with blood glucose disturbance as an additional parameter (IV). These results need further validation in a more heterogeneous population and in a multicentre study in which NEWS parameters and blood glucose are measured in all patients encountered by the EMS.

In previous studies with adding blood glucose into a “track and trigger” system almost all studies used logistic regression modelling. Cattermole et al. study results relied also on AUROC results and Glassberg et al. relied on likelihood ratios. These results need further validation in a more heterogeneous population and in a multicentre study in which NEWS parameters and blood glucose are measured in all patients encountered by the EMS.

The only other study of adding blood glucose to NEWS thus far has been conducted by Abbott et al. In this study blood glucose was separately studied as an addition to “track and trigger” system, not weighted as a model with an additional parameter depending on whether blood glucose reflected SIH, normoglycaemia, or spontaneous hypoglycaemia. All other studies have studied blood glucose with a different “track and trigger” system. As so, no valid comparison can be made between the current study of adding blood glucose as additional parameter to NEWS and previous studies conducted with blood glucose and “track and trigger” systems (IV).
6.3 Methodological aspects

6.3.1 Internal validity

The study was conducted in the same EMS system with highly trained EMS personnel and standard treatment protocols (I-IV). This provided internal validity of the results. The data gathered from EMS was vast and was obtained from a single electronic EMS database (II and IV). Mortality data is highly accurate in Finland because patients carry an individual identity number and causes of death are recorded in the Finnish Population Register Centre according to Finnish legislation.

Only in RCT studies can confounding factor truly be eliminated. Three studies were retrospective observational cohort studies (I, II, and IV). During the study period, data gathering was conducted at the same time as the electronic EMS database (Merlot Medi®) was implemented into the EMS system. Albeit a single person may find unexpected errors, this can also cause bias because there is no cross check from another researcher. To avoid this known bias, the data were extracted very meticulously to avoid any unnecessary errors. Individual difference in professional expertise, time of day or night, and other workload of personnel from EMS and Finnish Population Register Centre may have also affected how meticulously the study data were manually recorded into databases when data could not be automatically recorded. On the other hand, automatic recording was also prone to systematic errors that may cause bias.

Patient characteristics and underlying comorbidities, such as degree of imbalance in diabetes and varying nutritional status, together with current and chronic comorbidities, medication used during the episode, and possible influence of diurnal excretion of other hormones of the body, may cause a lack of internal validity. Physiological characteristics, such as peripheral vasoconstriction, acidosis, and artefacts caused by finger-tip capillary samples, may also cause a lack of internal validity. These confounding factors could not be taken thoroughly into consideration when interpreting results.

Technical equipment and protocols follow the same standard when operating with one single EMS system. However, although there were standard calibration frequencies for blood glucose metres, the time lag from calibration to encountering patient cases varied greatly which could have caused bias in interpretation of the results.
6.3.2 External validity

Blood glucose measurement is a simple, widely used biomarker recorded in the EMS. EMS personnel should become more aware that blood glucose disturbance has been associated with a more serious underlying problem during critical illness and can affect patients with diabetes as well as patients without diabetes 14.

Blood glucose disturbance has been extensively studied, and many of these studies have proven an association of SIH and spontaneous hypoglycaemia with higher mortality and morbidity 9–12. Patients who develop SIH during critical illness but do not have previously known diabetes and are characterized as having prediabetes are at an especially increased risk of mortality 50. After the positive results of the first Louven study, the landmark study of van Berghe, in 2001, the study results showing the benefit of treating SIH with insulin were implemented widely, and treatment protocols changed again after negative results were reported in 2009 from the NICE-SUGAR study results 13,61. Different study findings have resulted in a lack of external validity with no uniform consensus on how to measure and treat blood glucose disturbance. Although our findings provide some new knowledge (I-IV), our study results showing an association between poorer outcome (I) and hypoglycaemia encountered in critical ill patients (II) were mostly in concordance with previous study findings, giving some external validity to our results.

Although in most patient centres, blood glucose is a routine measurement, patient characteristics and cultural differences may vary. Geographically, the patient centre may have been in a different altitude, humidity, or climate temperature environment, which can affect patients and technical equipment. For instance, in Finland, alcohol abuse seems to be overly presented, which may influence our results (II). These confounding factors may decrease external validity.

Recent findings suggest that the underlying imbalance in diabetes affects the presentation of SIH and spontaneous hypoglycaemia, resulting in greater variability compared with patients without diabetes 55. Patients with prediabetes and acute critical illness with SIH seem to have an especially high mortality outcome. Variability seems to be a good new predictor for association with poorer outcome 257. Patients with and without diabetes have often been studied in the same study population. However, due to different underlying conditions regarding diabetes status, the study results have possibly lacked external validity. Depending on the study design, studying patients both with and without diabetes may also be appropriate. For instance, in Study IV, where blood glucose disturbance was added as an additional parameter to NEWS, diabetes status was irrelevant.
The current opinion is to try to find more individual treatment options that consider patient diabetes status. With all these factors taken into consideration, the results would have better external validity.

6.3.3 Study limitations

The main limitation was that three out of the four studies were retrospective (I, II and IV). In some parts, data needed to be manually recorded (I, II and III) because the first version of electronic EMS database was implemented when Study II was conducted. However, data were meticulously checked when gathered to avoid any bias. The study of OHCA patients had a very small sample size due to a difficult study design that hindered data collection (III). Hence, no causal relationship could be drawn from conclusions (III). Additionally, catecholamine and growth hormone levels were not measured; they are known to affect blood glucose disturbance (III). None of the studies had an actual control group for the study population (I-IV). Other limitations included the fact that blood glucose was not measured in all patients (I, II, and IV). Instead, the EMS has a local protocol that blood glucose is only measured in patients with a lowered level of consciousness, sudden deterioration of overall wellness from an unknown cause, disorientation or agitation, seizure or hypothermia or diabetic patients who are feeling unwell. Additionally, study design restrictions did not permit long-term follow-up (I-IV).

6.4 Clinical implications

This study highlights that blood glucose disturbance is not always caused by diabetes and that it should be recorded from all patients encountered by the EMS. On the one hand, when blood glucose disturbance is observed during acute critical illness regardless of diabetes status, the treating personnel should be aware that this type of blood glucose disturbance is common and on the other hand it is associated with higher mortality. Patients with prediabetes and SIH seem to be at the highest risk of poorer outcome. Blood glucose measurements seem to be beneficial when added to NEWS for better discrimination of risk of death. However, when using blood glucose as a parameter in a “track and trigger” system, blood glucose disturbance should be weight to categories: hyperglycaemia, normoglycaemia and spontaneous hypoglycaemia. This study also emphasized that the initial physiology underlying blood glucose disturbance may differ in the prehospital surroundings compared with blood glucose disturbance observed in the hospital. This indicates that interventions should possibly be targeted much earlier, in the prehospital setting.
6.5 Future studies

Although previous insulin intervention trials have had hypoglycaemia incidence rates too high, thus overruling positive treatment results, in the future, adequately powered and more individualized treatment designs utilizing advanced monitoring techniques should be conducted. Future studies should possibly use computerised dosing algorithms, constant blood glucose monitoring devices, and focus more on minimizing blood glucose variability as well as the time to target value over the peak or mean values. Patients with or without diabetes should be investigated separately if the study design allows it. A consensus on how the studies should be designed would lead to external validity of the results. Because insulin treatment requires close monitoring, staff are needed for titration of infusions. Giving native GLP-1-infusion or GLP-1 analogues could possibly be considered a new interesting novel intervention because it does not carry a hypoglycaemia risk. However, safety aspects need to be considered first when considering native GLP-1-infusion or GLP-1 analogues because there is a lack of sufficient knowledge regarding the possible pharmacological and pharmacokinetic interactions during critical illness, especially when renal or liver failure is present.
The present study addressed different aspects of blood glucose disturbance during critical illness encountered by the EMS. The study findings focused on describing blood glucose changes in STEMI-patients in the prehospital phase. How commonly hypoglycaemia is present in non-diabetics encountered by the EMS? What are the initial pathophysiological mechanisms in OHCA patients? Further, could blood glucose improve NEWS when added as an additional parameter for better discrimination of risk of death.

The conclusions were as follows:

1. Increasing blood glucose level in STEMI-patients, from the prehospital surroundings to hospital admission, was associated with a worse outcome, including increased short- and long-term mortality, increased infarct size and decreased cardiac function.

2. Hypoglycaemia without diabetes was commonly encountered by the EMS. Alcohol abuse, intoxication, and malnutrition were found to be the most likely causes related to hypoglycaemia. Hypoglycaemia together with critical illness encountered by the EMS was not very prevalent.

3. The very early physiological mechanisms of SIH seemed to differ from mechanisms studied in hospital surroundings. Although hyperglycaemia was present, insulin and glucagon were initially low in OHCA patients, along with marked interindividual variation in levels of the biomarkers insulin, glucagon, endogenous GLP-1, IL-6, and cortisol.

4. Adding blood glucose to standard NEWS seemed to improve discrimination of the risk of death, especially when hypoglycaemia was present.
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