Perioperative hyperglycaemia and its treatment in patients with diabetes mellitus

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INTRODUCTION AND OUTLINE OF THIS THESIS

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Before 1946, anaesthesia in the Netherlands mainly consisted of ether narcosis provided by the youngest surgical resident. However, in 1946 miss Doreen Vermeulen-Cranch introduced the endotracheal tube, routine intravenous access, muscle relaxants, intravenous analgesics, epidural and spinal anaesthesia as standard anaesthetic practices. She continued to innovate anaesthetic practice and a few years later, in 1958, became the first professor of anaesthesia in the Netherlands (1). In these early days perioperative monitoring barely existed and perioperative coma and death were not uncommon.

Fortunately, the field of anaesthesia evolved rapidly. The development of the oxygen monitor in 1972 and its subsequent perioperative use led to a 90% reduction of perioperative mortality (2). After this, not only new haemodynamic but also glycaemic monitoring devices have been implemented in routine perioperative care (3). Perioperative glucose monitoring, performed as point of care measurement or with a continuous glucose monitor, plays a central role in this thesis: Should we monitor glucose in patients without DM to diagnose 'stress hyperglycaemia'? Will these additional glucose measurements or implementation of a continuous glucose monitor result in better glycaemic control? And finally, how can we optimise the perioperative glycaemic management for the obvious group at risk for hyperglycaemia – the patient with diabetes mellitus (DM)?

PART 1. Perioperative glycaemic control

In general, patients with perioperative hyperglycaemia can be divided into three groups: approximately 30-50% of the patients with hyperglycaemia have DM, 25-30% of the patients have a form of pre-diabetes and will be diagnosed with DM in the next year, and 20-35% of the patients develop 'stress hyperglycaemia' due to a (surgical) stressor (4). Development of perioperative stress hyperglycaemia is the result of stress hormone up-regulation (e.g. adrenaline, noradrenaline and cortisol) along with simultaneous peripheral insulin resistance. It is unknown whether temporarily diminished betacell function also plays a role. Data from critically ill patients suggest that hyper- and hypoglycaemia are particularly harmful in patients without DM (5). However, it is hard to predict which patient will develop perioperative stress hyperglycaemia. Furthermore, other anaesthetic strategies like the frequent use of dexamethasone for the prevention of postoperative nausea and vomiting can also influence glucose homeostasis and induce transient hyperglycaemia (6).

In **PART 1** of this thesis we investigate whether 'stress hyperglycaemia' is associated with postoperative complications in the non-critically ill, surgical population.

Chapter 2 gives an overview of the prevalence of hyperglycaemia and contributing factors during ambulatory surgery. **Chapter 3** focusses on patients undergoing gynaecologic laparotomies and the role of hyperglycaemia on postoperative complications. Taken together, these chapters contribute on our knowledge on whether we should monitor perioperative glucose in patients without DM.

During ambulatory as well as during major surgery, dexamethasone is widely used by anaesthesiologists to prevent postoperative nausea and vomiting. Whether this practice leads to perioperative hyperglycaemia and an increased risk of infections is reviewed in **Chapter 4** using a meta-analysis approach.

Glucose homeostasis is maintained via a complex network of hormones, which in their turn regulate enzymatic processes to keep glucose within strict boundaries (4.4-5.6 mmol l^{-1}). A defect in one of these pathways can have major consequences. At the end of PART 1, the disease 'very-long-chain-acyl-CoA dehydrogenase deficiency (VLCADD)' is discussed. Patients with VLCADD are vulnerable to hypoglycaemic episodes due to the enzyme deficiency when they are fasted or stressed. Furthermore, several anaesthetics are supposedly contraindicated in patients with VLCADD. An overview of the perioperative glycaemic management (with a continuous glucose monitor) and anaesthetic management for patients with VLCADD is given in **Chapter 5**.

PART 2. Perioperative management of patients with diabetes

Part 2 of this thesis focusses on the perioperative management of patients with DM. In 2025, the worldwide prevalence of DM will have increased to 300 million people (7). Because DM is accompanied by macro- and microvascular complications, patients with DM are more likely to be admitted to a hospital, which translates into a prevalence of DM in hospitalised patients of up to 40% (8). Also, the annual risk of needing surgery is two to six fold increased in patients with DM as compared to patients without DM (9). Interestingly, many guidelines have been published on the perioperative management of DM, but most statements in these guidelines are based on expert opinion (10,11).

Chapter 6 gives an overview of the perioperative management of diabetic patients. Although this review focusses on patients presenting for ambulatory surgery, much of the statements made in this review are based on literature from patients presenting for in-patient (major) surgery.

Twenty years ago, all details of the anaesthetic management were recorded by hand on a paper form, while nowadays most hospitals in the Netherlands use an electronic data management system. We were able to install automated reminders to optimise perioperative anaesthetic or diabetes management within these electronic data management systems. **Chapter 7** looks at the effect of such a reminder on perioperative adherence to our diabetes protocol.

A challenge in the perioperative management of patients with DM appears to be the hourly glucose measurements, which are time consuming and thus omitted/forgotten frequently. In **Chapter 8** we assessed whether a continuous glucose monitor improved perioperative glucose control compared to standard care with hourly glucose measurements.

Most patients with diabetes type 2 will start with metformin treatment (13). Common practice is to cease metformin before surgery, an advice based on the fear for development of lactate acidosis. However, retrospective data suggested that the risk for lactate acidosis might be overestimated. Therefore, in **Chapter 9** we evaluated whether continuing metformin during the perioperative period lowers pre- and postoperative serum glucose without causing a significant increase in plasma lactate.

The mechanism of action of glucose lowering drugs differs significantly between different classes of drugs. As this remains an active field of research, novel treatment options for DM are becoming available. Novel options for the treatment of DM also implicate possible new strategies for the perioperative management of DM. **Chapter 10** describes a randomised controlled trial in which we investigated the feasibility of premedication with a glucagon like peptide-1 (GLP-1) agonist for perioperative glucose control.

Long-term dysregulation of glucose values puts patients with DM at risk for organ damage, like nephropathy, retinopathy and neuropathy. This thesis is concluded by an observational study on autonomic neuropathy in patients both with and without DM. In **Chapter 11** the relevance of diagnosing autonomic neuropathy in patients with DM in order to be able to predict haemodynamic instability during anaesthesia is assessed.

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