What goes up must come down: glucose variability and glucose control in diabetes and critical illness
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Chapter 1

Introduction

Sarah E. Siegelaar
Glucose: essential for life but harmful in excess. Because of this paradox, the glycaemic balance is a tightly regulated feed-back system in the healthy human body; unrestrained increases in plasma glucose are prohibited by the action of insulin, and counterregulatory hormones, such as glucagon, prevent plasma glucose to decrease to dangerously low levels. As a result, plasma glucose levels in healthy humans almost never exceed 7.8 mmol/l; the upper limit of what is considered normal. There are, however, conditions where this equilibrium is being disturbed, resulting in chronic as well as acute hyperglycaemia. Hyperglycaemia is known to induce endothelial damage, probably because a mitochondrial glucose overload leads to formation of free oxygen radicals, so-called oxidative stress, but the exact pathophysiology is not fully elucidated yet. This thesis pictures different types of hyperglycaemia and examines whether hyperglycaemia is always harmful and, as a result, should by all means be avoided.

Chronic hyperglycaemia is the defining feature of diabetes mellitus, as a result of an absolute (type 1 diabetes mellitus) or relative (type 2 diabetes mellitus) shortage of insulin. It affects the micro- and macrovasculature, causing damage to multiple organs. We know it is beneficial for patients with diabetes to decrease the high glucose values and aim at HbA1c values below 7% for newly diagnosed patients and perhaps somewhat less strict for patients with established disease and complications. This seems straightforward, but unfortunately, it is not that easy. Patients with similar mean glucose or HbA1c levels can have markedly different daily glucose profiles, with differences both in number and duration of glucose excursions; so called glucose variability, the topic of Part I of this thesis.

It has been suggested that high glucose variability induces vascular damage independent from average glycaemia, which would have consequences for diabetes treatment. In Chapter 2 an overview of different glucose variability measures is given and the current literature regarding its effects in various populations is reviewed. To better understand the effect of glucose variability, in Chapter 3 we studied whether the effects of mild hyperglycaemia on vascular homeostasis are glucose-dependent or have a threshold above which damage starts. The independent effect of glucose variability on oxidative stress is investigated in Chapter 4 and Chapter 5, including type 2 diabetes patients treated with oral glucose lowering drugs or insulin, respectively. A more clinical question is addressed in Chapter 6 where datasets of the large Diabetes Control and Complications Trial (DCCT) were reanalysed to assess the effect of glucose variability on the development of neuropathy in type 1 diabetes. In Chapter 7 we describe the first trial that specifically lowered glucose variability in type 2 diabetes patients assessing the effect on future cardiovascular event rates.
That glucose homeostasis can be disturbed during critical illness is discussed in Part II of this thesis. This so called "stress-hyperglycaemia" due to inflammatory and neuro-endocrine derangements, is common in critically ill patients and associated with mortality. In 2001, van den Berghe et al. startled the intensive care community by publishing the results of a randomised controlled trial investigating the effect of intensive insulin therapy on outcome, which showed that lowering plasma glucose to normoglycaemic levels dramatically decreased mortality. But again, practice seemed not to be as easy as proposed: the results from van den Berghe et al. could not be reproduced and accumulating evidence suggests that the use of intensive insulin therapy is perhaps even harmful in some patients. In Chapter 8 the optimal target range for mean glucose during intensive care unit admission is explored further.

As heavy the disagreement is on whether strict or less-strict glycaemic control should be applied in the intensive care unit, all are united that marked hyperglycaemia and severe hypoglycaemia should be avoided. At present, time-consuming intermittent blood sampling has to be performed to achieve glycaemic control, and moreover, no information is available about glucose values in-between measurements. Subcutaneous continuous glucose monitoring (CGM) could therefore be of value in achieving glycaemic control. However, accuracy and reliability of the available systems seems uncertain in critically ill patients. Therefore, we performed a head-to-head comparison of two subcutaneous CGM systems in patients admitted to the intensive care unit after cardiac surgery, presented in Chapter 9. The sometimes decreased accuracy of subcutaneous CGM systems in the critically ill might result from alterations in the microcirculation because needle-type glucose sensors measure glucose in the interstitial fluid and not directly in blood. This has been investigated in Chapter 10, where the microcirculation and its relation with continuous glucose sensor accuracy were studied in cardiac surgery patients.

Not all patients with critical illness-induced hyperglycaemia are similar. More and more the idea evolves that chronic hyperglycaemia in critically ill patients with diabetes is pathophysiologically different from acute hyperglycaemia in those without previously diagnosed diabetes. This could mean that treatment targets and strategies should differ between these populations. The relation between hyperglycaemia and mortality as well as the effect of intensive insulin therapy in critically ill patients with diabetes is discussed in Chapter 11. Finally, in Chapter 12 the results of a meta-analysis looking at differences in mortality between patients with and without diabetes when admitted to the intensive care unit are shown, which allows us to put acquired knowledge into perspective.

In the end, this thesis is about glucose peaks and their consequences: must all what goes up come down?
References