Hypoglycaemia in diabetes
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Citation for published version (APA):
Schopman, J. E. (2013). Hypoglycaemia in diabetes

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CHAPTER 1

INTRODUCTION
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“Insulin is not a cure for diabetes, but it is a potent preparation, alike for evil and for good.”

The above observation was made in the 1920s by Joslin and his colleagues in response to their early clinical experience with the use of insulin, which had been discovered shortly before in Toronto by Frederick Banting and John Macleod. Initial use of pancreatic extracts had caused “toxic” reactions, some of which were later to be identified as ‘hypoglycaemia’. Ninety years after the discovery of insulin, despite many advances in insulin therapy and patient education, hypoglycaemia is still a major impediment to diabetes treatment. Hypoglycaemia may be experienced as an unpleasant or frightening sensation by the affected individual and disrupt several aspects of everyday life. It is important to realise that hypoglycaemia is often unpredictable and may occur at any time of day or night.

Hypoglycaemia means low blood glucose but is difficult to define in more detail. Firstly, what constitutes a low blood glucose level is disputed, with glucose cut-off levels varying between 2.8 mmol/L and 3.9 mmol/L. Secondly, hypoglycaemia can range from asymptomatic through distressing to disabling and even life-threatening. Symptoms of hypoglycaemia are manifold and most are non-specific, i.e. they may occur in other conditions. Besides, not all patients with diabetes experience symptoms when their blood glucose levels are low. Severe hypoglycaemia without symptoms was recognised as a clinical problem early in the course of treatment with insulin. Therefore, the most commonly used definitions of hypoglycaemia are mild and severe hypoglycaemia. Mild hypoglycaemia is defined as an episode of hypoglycaemia which is successfully treated by the patient alone. Severe hypoglycaemia is considered to occur when help from another person is needed to treat an episode of hypoglycaemia.

Recurrent exposure to hypoglycaemia may cause the development of a diminished symptomatic warning leading to difficulty in detecting the onset of hypoglycaemia, a condition which is known as “impaired awareness of hypoglycaemia”. The exact aetiology of the acquired syndrome of impaired awareness of hypoglycaemia is unknown and may be partially explained by adaptation of the central nervous system to hypoglycaemia. When impaired awareness of hypoglycaemia is present, a vicious circle may arise, with episodes of hypoglycaemia leading to more episodes of hypoglycaemia, which increases the risk of severe hypoglycaemia even further.

The prevalence of impaired awareness of hypoglycaemia in a cohort of patients with type 1 diabetes is described in chapter 2. Not only the patients with impaired awareness of hypoglycaemia suffer from asymptomatic hypoglycaemia; patients with normal awareness
also have asymptomatic hypoglycaemic episodes, which is described in chapter 3. Chapter 4 describes the prevalence of impaired awareness of hypoglycaemia in people with insulin-treated type 2 diabetes.

At home, hypoglycaemia may be detected using capillary home blood glucose monitoring, which is the standard of glucose monitoring in everyday life. The detection of hypoglycaemia using capillary testing is limited by its dependency on the frequency and timing of testing and whether the individual has any symptoms of hypoglycaemia. Many episodes of asymptomatic hypoglycaemia will therefore be missed. Some consider the use of continuous glucose monitoring systems as a ‘gold standard’ for the detection of (asymptomatic) hypoglycaemia. Chapter 5 gives an overview of the literature on the impact of continuous subcutaneous insulin infusion and continuous glucose monitoring systems on the occurrence of hypoglycaemic events compared to standard treatment (multiple daily injections or home blood glucose monitoring) in patients with type 1 diabetes. In chapter 6 the results are shown of a systematic review and meta-analysis assessing the accuracy of continuous glucose monitoring systems for hypoglycaemia detection as compared to home blood glucose monitoring using conventional glucose meters and/or laboratory devices in people with type 1 diabetes.

Although hypoglycaemia is mainly a concern for patients on insulin therapy, hypoglycaemia can also be a side effect of oral glucose lowering medications. This is most common with insulin secretagogues such as sulfonylurea derivatives. A systematic review and meta-analysis assessing the proportion of patients with type 2 diabetes that experience hypoglycaemia when treated with a sulfonylurea can be found in chapter 7.

Besides the awareness of the patient for the detection of hypoglycaemia, the awareness of hypoglycaemia of the care provider is also of major importance. Chapter 8 explores factors such as hypoglycaemia that influence the decision-making behaviour of care providers with regard to basal insulin dose adjustments in patients with type 2 diabetes.

The counterregulatory response to hypoglycaemia, with glucagon as the most important mediator is diminished within a few years of the onset of type 1 diabetes and subsequently lost. This exacerbates the risk for hypoglycaemia associated with the administration of insulin. The exact aetiology of this diminished glucagon response to hypoglycaemia is unknown since the secretory response of the pancreatic α-cells to release glucagon to other stimuli than hypoglycaemia is still intact. Chapter 9 explores whether a relatively new drug, a dipeptidyl peptidase 4 inhibitor, could restore the glucagon response to hypoglycaemia in patients with type 1 diabetes.
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Hypothermia has been associated with acute hypoglycaemia since the earliest use of insulin to treat diabetes \(^1\). The intrinsic mechanism is still not fully known. A counterintuitive increase in heat production is observed during hypoglycaemia which is likely to be mediated by sympathetic innervation. Brown adipose tissue, which has recently been recognised to be a heat-producing organ, is stimulated by norepinephrine released from the sympathetic nervous system. The effect of hypoglycaemia, with its concomitant sympatho-adrenal response, on the uptake of the labelled glucose analogue \(^{18}\)F-fluorodeoxyglucose in brown adipose tissue using positron emission tomography and computer tomography is described in chapter 10.

Chapter 11 summarises the most important findings of this thesis and provides suggestions for future directions of research. A Dutch language summary can be found in chapter 12.

REFERENCES


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