CHAPTER 11

SUMMARY AND FUTURE DIRECTIONS
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Hypoglycaemia and impaired awareness of hypoglycaemia are common, increase the risk of severe hypoglycaemia and have a major impact on patients’ perceived health and well-being. This thesis focuses on the prevalence of impaired awareness of hypoglycaemia in type 1 diabetes and in insulin-treated type 2 diabetes and attempts to provide further insight into the pathophysiology of hypoglycaemia. Potential methods of monitoring glycaemia are assessed and the potential of new drug therapies (DDP-4 inhibitors) to influence counterregulation to hypoglycaemia is studied.

Chapter 2 shows that twenty percent of patients with type 1 diabetes in a large Scottish cohort are affected by impaired awareness of hypoglycaemia. Compared to those with normal awareness of hypoglycaemia, those with impaired hypoglycaemia awareness had a six-fold higher incidence of severe hypoglycaemia in the previous year. This suggest that the prevalence of impaired awareness of hypoglycaemia has remained stable over the past decades, despite the introduction of novel therapies such as treatment with insulin analogues and multiple daily injections.

Chapter 3 confirms that adults with type 1 diabetes who have impaired awareness of hypoglycaemia are exposed to a much higher incidence of asymptomatic hypoglycaemia than those with normal awareness. In this study a group of 19 patients with type 1 diabetes with normal hypoglycaemia awareness were matched for age, sex, duration of diabetes and glycaemic control with 19 patients with impaired awareness of hypoglycaemia. Asymptomatic hypoglycaemia episodes accounted for 47% of all hypoglycaemia values in the group with impaired awareness, compared to 14% in the group with normal awareness of hypoglycaemia.

Chapter 4 shows that around ten percent of the insulin-treated type 2 diabetes patients are affected by impaired awareness of hypoglycaemia. Those with impaired awareness of hypoglycaemia experienced nearly two and a half episodes of mild hypoglycaemia per month, which was a fivefold higher incidence than those with normal hypoglycaemia awareness. On average, nearly one episode of severe hypoglycaemia in the preceding year was experienced per patient with impaired awareness of hypoglycaemia which was 17-fold higher than those with normal hypoglycaemia awareness. Diabetes care providers should be aware of the occurrence of impaired awareness of hypoglycaemia in insulin-treated type 2 diabetes patients.

Views differ regarding the most appropriate methods and situations in which evaluation of awareness of hypoglycaemia should be undertaken. These range from the use of
questionnaires and utilisation of continuous glucose monitoring to identification of symptom generation during experimental hypoglycaemia using glucose clamps. Although the latter method allows for detailed assessment of all variables, there are a number of limitations since the experimental setting is not representative of everyday ambulatory conditions and the way of inducing hypoglycaemia is artificial. The subject may anticipate the generation of symptoms and on the other hand attenuation of symptoms occurs when lying flat during the experiment.

The research described in this thesis used questionnaires to translate the opinion from patients who have daily experience with insulin and exposure to hypoglycaemia. The method by Gold et al. was used to assess impaired awareness of hypoglycaemia, which asks the question: “do you know when your hypos are commencing?” The respondent selects a number on a 7-point Likert scale with 1 representing “always aware” and 7 representing “never aware”. A score of 4 or more is designated as impaired awareness of hypoglycaemia. This single item scale is brief, feasible and validated, but does not provide room for a more delicate distinction of features of impaired awareness of hypoglycaemia such as the difference between awareness of hypoglycaemia when awake and asleep. Speight and colleagues have recently developed a new questionnaire to assess impaired awareness of hypoglycaemia with input from patients with type 1 diabetes. It consists of 18 items and may be more sensitive to identify a change in awareness status. This new method to assess awareness of hypoglycaemia requires further evaluation but may be very useful in clinical trials and may enable better recognition of impaired awareness of hypoglycaemia. However, it takes a median time of 7 minutes to complete the questionnaire. It might therefore be too extensive to incorporate in clinical practice.

Continuous glucose monitoring (CGM) could be a useful tool to prevent hypoglycaemia. Previous randomised controlled trials have failed to show an effect of continuous glucose monitoring systems on the occurrence of (severe) hypoglycaemia, but these were designed to show an effect on haemoglobin A1c and not to ascertain how they would affect the frequency of hypoglycaemia or the state of hypoglycaemia awareness. Besides, patients who were at a high risk of developing severe hypoglycaemia were mostly excluded from these trials. Chapter 5 and chapter 6 give an overview of the currently available evidence for the detection of hypoglycaemia with these systems. The performance of continuous glucose monitoring devices seems to be less accurate and reliable during hypoglycaemia than during eu- and hyperglycaemia. Systematic review of published studies showed that the diagnostic accuracy of continuous glucose monitoring devices for the detection of hypoglycaemia was low to moderate.
The preliminary results of a randomised controlled trial in the UK (the Hypo COMPASS trial) of people with type 1 diabetes who have impaired awareness of hypoglycaemia, comparing hypoglycaemia avoidance with or without real time continuous glucose monitoring with multiple daily injections or continuous subcutaneous insulin infusion (CSII) were presented in June 2013 at the annual American Diabetes Association meeting in Chicago. The primary outcome measure for this study was the difference in hypoglycaemia awareness status measured by the method of Gold et al. and the secondary outcomes included severe hypoglycaemia incidence, glycaemic control, number of minutes per day spent in biochemical hypoglycaemia as measured by blinded CGM and patient satisfaction. At 24 weeks there were no statistically significant differences between the four groups in hypoglycaemia awareness status, the incidence of severe hypoglycaemia episodes, glycaemic control and the number of minutes per day spent in biochemical hypoglycaemia. Overall the median Gold score improved and the number of minutes per day spent in biochemical hypoglycaemia declined significantly. Patients that were treated with CSII were more satisfied, but there was no difference in patient satisfaction between those that monitored their blood glucose with CGM compared to those that performed capillary blood glucose measurements. We may now conclude that continuous glucose monitoring is not superior to home blood glucose monitoring for the prevention of hypoglycaemia in patients with type 1 diabetes. The accuracy of CGM needs improvement to detect hypoglycaemia with greater reliability and future technical developments for continuous glucose monitoring systems should focus on the problem of hypoglycaemia from the patient’s perspective.

Sulfonylurea derivatives, which act by increasing insulin release from the β-cells in the pancreas, may also cause hypoglycaemia in patients with type 2 diabetes. Chapter 7 presents the results of a systematic review and meta-analysis assessing the proportion of patients with type 2 diabetes mellitus that experience hypoglycaemia when treated with sulfonylurea. In total, 22 studies were included containing approximately 6,000 patients. The meta-analysis showed that the vast majority of patients with diabetes type 2 treated with a sulfonylurea derivative with or without a combination with metformin remains free of any relevant hypoglycaemia during the study periods. Approximately ten percent of the patients experienced mild hypoglycaemia with a plasma glucose ≤3.1 mmol/L and severe hypoglycaemia was experienced by less than one percent of the patients. The meta-analysis showed that a lower proportion of type 2 diabetes patients taking gliclazide experienced a mild hypoglycaemic event (1.4%) when compared to patients taking glimepiride (15.5%) and that a lower proportion of patients taking gliclazide (0.1%) experienced severe hypoglycaemia compared to glipizide (2.1%), while a similar trend was observed for gliclazide vs. glimepiride (0.9%). Sulfonylureas stimulate insulin secretion
by closing ATP-sensitive K$^{+}$-channels in the β-cells of the pancreas. However, these ATP-sensitive K$^{+}$-channels are also present in myocardial cells. Gliclazide is unique in this respect, because it selectively inhibits ATP-sensitive K$^{+}$-channels in the pancreas. In a retrospective cohort study from Canada with 11,274 patients with type 2 diabetes with previously diagnosed acute coronary syndrome, gliclazide use was associated with a lower risk of hospitalization and mortality due to new acute coronary syndrome events compared to glyburide use. Patients with diabetes that have chronic kidney disease treated with sulfonylurea have an increased risk of hypoglycaemia associated with reduced clearance of the sulfonylurea or their active metabolites, thus necessitating a decrease in drug dosing to avoid hypoglycaemia. Gliclazide is cleared by the kidneys, but is metabolised in the liver. Therefore, no dose adjustments are needed for gliclazide treatment in patients with chronic kidney disease. Overall gliclazide seems to have a more favourable profile than other sulfonylurea. Therefore, gliclazide should be more frequently chosen as a comparator in active comparator studies of new lowering drugs in the future.

How patient factors such as hypoglycaemia influence the decisions of diabetes care providers to adjust the basal insulin dose of their patients with type 2 diabetes is shown in chapter 8. To investigate this, vignettes of representative clinical scenarios were used. Five hundred twenty paper questionnaires were distributed among Dutch physicians and nurses in primary and secondary care. For each vignette, respondents were asked to indicate whether they would advise to change the insulin dose and write down their rationale. One hundred and ninety questionnaires were returned (37%). Overall the occurrence of a hypoglycaemic event in a vignette led to a decrement of basal insulin dose. In case of a severe hypoglycaemic event compared to a mild hypoglycaemic event, care providers were nearly five times more likely to decrease the insulin dose. The decision to lower the insulin dose was taken irrespective of the glucose value that was mentioned in the clinical scenario. Even when a euglycaemic value was presented in combination with hypoglycaemic symptoms (relative hypoglycaemia), the decision to lower the insulin dose was taken. Insight in the practical implementation of basal insulin therapy by care providers is valuable information to re-form guidelines. Future research should be undertaken in other countries to establish whether the findings of the present study are universal.

Glucagon is the most important mediator of the counterregulatory response to hypoglycaemia. In patients with type 1 diabetes the ability to secrete glucagon during hypoglycaemia is progressively impaired and this increases the risk for hypoglycaemia which is associated with the use of insulin. Administration of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) in healthy individuals have been
shown to increase glucagon responses during hypoglycaemia\textsuperscript{19, 20}. Through the inhibition of dipeptidyl peptidase 4 (DPP-4) the plasma levels of GIP and GLP-1 are increased. Chapter 9 studies the effect of sitagliptin, a DPP-4 inhibitor, in 16 type 1 diabetes patients on glucagon and/or catecholamine counterregulatory responses to hypoglycaemia. Sitagliptin treatment significantly increased levels of both intact GLP-1 and GIP, but no significant differences were observed for glucagon or catecholamine counterregulatory responses. The secretory response of glucagon by the pancreatic α-cells to other stimuli seems to remain intact: glucagon is still secreted in response to exercise and arginine infusion\textsuperscript{21}. This is consistent with the premise that the impaired glucagon response to hypoglycaemia in type 1 diabetes probably reflects abnormal intrinsic signalling rather than a structural defect in the α-cells of the pancreas. Future research should be undertaken to identify the signal that leads to the secretion of glucagon during hypoglycaemia in order to find a solution for this defective response.

Hypothermia has been associated with acute hypoglycaemia since the earliest use of insulin to treat diabetes\textsuperscript{22}. During hypoglycaemia core temperature falls, but heat production seems to increase\textsuperscript{23, 24}. Brown adipose tissue, which is present in adult humans in quantities that may contribute to non-shivering thermogenesis, is activated by cold exposure. The sympathetic nervous system seems in control of both the activity of brown adipose tissue and heat production during hypoglycaemia\textsuperscript{23, 24}. The activity of brown adipose tissue during euglycaemia and hypoglycaemia in a moderately cold environment is studied in chapter 10 with the use of the labelled glucose analogue 18F-fluorodeoxyglucose using positron emission tomography and computer tomography. The amount of 18F-fluorodeoxyglucose uptake in brown adipose tissue during hypoglycaemia was similar when compared to euglycaemia. This could imply that brown adipose tissue activity is not a major determinant of the increased heat production that occurs during hypoglycaemia. However, the study design could have been improved by small modifications such as measurement of the resting energy expenditure and continuous core and skin temperature measurements of the subjects. Additional experiments in thermoneutrality may help to separate the effect of cold on the activity of brown adipose tissue. Furthermore, it is known that fatty acids are the main substrate for brown adipose tissue, while uptake of 18F-fluorodeoxyglucose, a glucose analogue, is used as a measure of brown adipose tissue activity. It is possible that brown adipose tissue in a hypoglycaemic condition uses relatively more fatty acids than glucose. Hence, brown adipose tissue activity might have increased, although this could not be visualized. The study should therefore be repeated with labelled fatty acids instead of a labelled glucose analogue. Future research in humans is required to elucidate how relevant the activity of brown adipose tissue is for human metabolism.
Hypoglycaemia remains a serious side effect of the treatment of diabetes. Therefore, ongoing research is required into the pathophysiology and clinical consequences of hypoglycaemia and impaired awareness of hypoglycaemia.

REFERENCES


