Closing the loop, squaring the circle: Studies on insulin delivery, glucose monitoring and the artificial pancreas

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Chapter 1
DIABETES IS ON THE RISE

Ever since it’s first documented description 1 century A.D. by the Greek physician Arataeus, the incidence of diabetes has grown to epidemic proportions in the present era. The World Health Organization estimates that 347 million people worldwide suffer from it (1). In the times of Arataeus, little could be done by a physician to cure or alleviate the disease and the lifespan of patients with diabetes was severely limited. Unfortunately this remained so for many centuries until 1921 when Sir Frederick Banting and his assistant Charles Best managed to keep a dog with diabetes alive by injecting it with canine pancreas extract. The work of Naunyn, Minkowski, Opie, Schafer, and others had shown that diabetes was caused by lack of a protein hormone secreted by the islands of Langerhans in the pancreas. Banting suspected that this hormone named insulin, after the latin word for island; *insula*, could perhaps be won from pancreatic tissue and used to treat patients. The first patient to receive this purified insulin extract was a young boy named Leonard Thompson on January 11th 1922, which instantly normalized his dangerously high blood glucose levels. The discovery of insulin has saved the lives of countless of patients with diabetes ever since. Fast-forward to current times and insulin is still the cornerstone of the treatment of type 1 diabetes (2). Although our understanding of insulin and its actions in the human body has increased and current technologies allowed us to create insulin in the laboratory with tailored pharmacodynamic profiles, the burden of insulin treatment on patients with type 1 diabetes is great and non-compliance may lead to the development of long-term complications, for which even compliant patients are at risk (3). This burden is mostly caused by the intensive involvement patients must have in their own insulin treatment which relies on frequent measurement of blood glucose values and appropriate decisions on insulin dosing. For more than half a century, scientists have been looking for a way to take this responsibility away from patients by designing an apparatus which automatically measures glucose levels and automatically administers the correct amount of insulin (4). To reach this goal, many aspects of glucose control and insulin administration still need to be addressed. In **PART I** of this thesis the effects of mealtime on glucose levels are assessed. The ingestion of a meal has traditionally been one of the most difficult challenges for
closed loop control (4,5). Chapter 2 describes the benefits of delivering insulin 15 minutes before the meal, thereby mimicking as closely as possible, the body’s natural insulinaemic response to a meal. The fact that the ingestion of a meal is not only one of the greatest challenges of closed loop control, but indeed one of the greatest challenges for a healthy pancreas, is proven by the extensive use of the Oral Glucose Tolerance Test in which a glucose load comparable to a meal is simulated and the insulinaemic response is measured. A diminished insulinaemic response leads to abnormal postprandial glucose levels, which in turn provides an excellent detection method for (pre-) diabetes which is discussed in Chapter 3. One of the other challenges of closed loop control is accurate and reliable administration of insulin. In PART II the importance of accurate insulin administration is investigated. Chapter 4 discusses how insulin pens have improved the reliability and accuracy of insulin dosing when compared to conventional insulin syringes, while Chapter 5 discusses the differences between patch-pumps with a very short internal insulin catheter versus conventional pumps with longer catheters and the effect of the age of the catheter infusion site on the absorption of insulin and subsequent its effects on postprandial glycaemia. Arguably the greatest challenge of closed loop control lies in the development of accurate and reliable continuous glucose monitoring (CGM) systems (6-11). PART III investigates these CGM systems. In Chapter 6 an overview is given on the effects of CGM on glucose regulation in various patient populations. Chapter 7 investigates the importance of the method of accuracy assessment and shows the difference between assessment of accuracy over a longer period at home, versus assessment at the clinical research centre (CRC). Chapter 8 continues on the knowledge gathered in chapter 7 to assess the accuracy of the three most used CGM systems. In PART IV the knowledge gathered and described in the previous chapters are combined and culminate in the accomplishment of closed loop control. In Chapter 9 we describe a near full day, automated closed loop intervention and assess technical feasibility and glycaemic control.
With the title of this thesis “Closing the loop, squaring the circle” reference is made to the age old challenge posed by geometers to construct a square with the same area as a given circle by using only a finite number of steps with compass and straightedge. This task was proven impossible in 1882 and “squaring the circle” has come into use as a description of trying to complete an impossible task. Like many geometers have tried to square a circle, many medical scientists have tried to close the loop. In closing the loop, glucose measurement, decision algorithms and insulin administration have to come together in a perfect fashion into a single device. However, unlike the science of geometry, medicine does not allow us to prove the impossibility of closing the loop simply by solving an equation on a piece of paper. Human nature allows us to push forward in matters of scientific uncertainty. Therefore the seemingly impossible might simply become a challenge.
Chapter 1

REFERENCE LIST


