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Closed loop insulin delivery in diabetes

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The primary goal of type 1 diabetes treatment is attaining near-normal glucose values. This currently remains out of reach for most people with type 1 diabetes despite intensified insulin treatment in the form of insulin analogues, educational interventions, continuous glucose monitoring, and sensor augmented insulin pump. The main remaining problem is risk of hypoglycaemia, which cannot be sufficiently reduced in all patient groups. Additionally, patients' burn-out often develops with years of tedious day-to-day diabetes management, rendering available diabetes-related technology less efficient. Over the past 40 years, several attempts have been made towards computer-programmed insulin delivery in the form of closed loop, with faster developments especially in the past decade. Automated insulin delivery has reduced human error in glycaemic control and considerably lessened the burden of routine self-management. In this chapter, data from randomized controlled trials with closed-loop insulin delivery that included type 1 diabetes population are summarized, and an evidence-based vision for possible routine utilization of closed loop is provided.

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Introduction

Type 1 diabetes is one of the most common chronic diseases in young people [1], and represents a considerable burden for affected individuals and society [2]. From the middle of the 20th century, a number of populations showed an upturn in the incidence of type 1 diabetes [3,4]. The current overall rate of increase in Europe is about 3–4% per annum, with the most rapid increase in children aged 0–5 years, and the incidence in children in this age group is expected to double by 2020 [5].

Intensive insulin therapy is considered to be the standard treatment for type 1 diabetes [6,7]; however, maintaining near normoglycaemia, a recommendation proposed by the Diabetes Control and Complication Trial more than 21 years ago [8], is proving difficult [9–11] The main problem is the risk of hypoglycaemia, which is a terrifying acute complication [12] [13], along with considerable disease-related burden [14–16].

Modern insulin pumps initiated the re-entry of advanced technology into diabetes management and considerably improved patients' wellbeing as well as metabolic control [17]. Real-time continuous glucose monitoring (CGM) measuring interstitial glucose levels was first tested in a randomized controlled trial (RCT) in 2006 [18], and subsequently in several RCTs demonstrating its efficacy in reducing HbA1c [19], time spent in hypoglycaemia [20] and severe hypoglycaemia [21]. Pairing with an insulin pump can improve glycosylated haemoglobin [22,23] and decrease time spent in hypoglycaemia [23]. The risk of hypoglycaemia is further mitigated by the use of low-glucose threshold insulin suspend feature [24,25], albeit not completely eliminated even with this latest routinely available technology.

Attempts towards computer-programmed insulin delivery have been made over the past last 40 years. The first use of machine-programmed insulin delivery goes back to the 1970s, with reports of improved states of metabolic control [26,27]. Closed-loop insulin delivery today most commonly links subcutaneous CGM with an external insulin pump through computerized control algorithms, which dictate insulin delivery in response to glucose sensor data [28,29]. The first 'modern' feasibility clinical trial comparing CGM and insulin pump with closed-loop insulin delivery was published in 2006, with increased time in target glycaemic range during closed loop, and no significant difference in mean blood glucose levels [30].

Two types of closed-loop systems are being tested: single-hormone closed loop, which delivers solely insulin, and dual-hormone closed loop, which delivers insulin and glucagon mini-boluses [31]. Several hybrid closed-loop systems, using manual boluses for covering meals, are also being investigated [32].

In this chapter, an overview of current data from RCTs comparing closed-loop insulin delivery with routinely available combination of an insulin pump and CGM therapy is provided.

Data source

All articles found in MEDLINE between January 2004 to September 2014 that contained the words 'closed loop' or 'artificial pancreas' and 'type 1 diabetes' were screened on October 1 2014 (Fig. 1). Criteria for inclusion were RCTs comparing closed-loop insulin delivery and combined CGM with continuous subcutaneous insulin infusion (CSII) or with sensor augmented insulin pump (SAP), in participants with type 1 diabetes. The following variables of metabolic control had to be reported: mean glucose levels or time within the target range (as defined by the investigators), time spent in hypoglycaemia (as defined by the investigators) or time spent in severe hypoglycaemia (as defined by the investigators) as primary end points, along with measures of glucose variability as secondary end points. Finally, 22 papers were included in the main comparison.

Time in target glycaemic range

Twenty-two trials presenting data from 518 patients with type 1 diabetes reported diverse results (Table 1).

The first RCT comparing closed loop with SAP, reported in 2010, included 19 children and adolescents with type 1 diabetes. The trial comprised three RCTs, but only two compared closed loop with SAP: the first during overnight glycaemic control and the second during overnight glycaemic control after physical activity in the afternoon. Significantly ($p = 0.00225$) more time was spent in target glycaemic range during closed loop than during SAP in both studies [33].