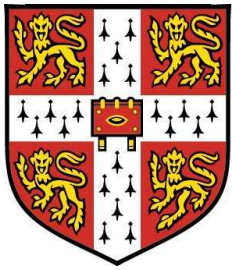
# Closed-Loop Insulin Delivery in Adults with Type 1 Diabetes



Kavita Kumareswaran

Wolfson College

Department of Medicine

University of Cambridge

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*This dissertation is the result of my work and includes nothing which is the outcome of work done in collaboration except where specifically indicated in the text. Any errors in this dissertation are mine alone. No part of this work has been submitted for any other qualification. The length of this dissertation lies within the word limit set by the Degree Committee of Clinical Medicine.*

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“The end of education is character." – Sai Baba

# Abstract

Achieving tight glucose control safely in type 1 diabetes with currently available methods of insulin delivery is challenging. Aggressive regimens carry an increased risk of hypoglycaemia, particularly overnight. Both alcohol consumption and exercise predispose further to low glucose levels. The demands are even greater in pregnancy where, in addition to limiting hypoglycaemia, avoidance of postprandial hyperglycaemia is critical to minimising adverse obstetric outcomes. The aim of my studies was to evaluate feasibility and safety of a closed-loop or 'artificial pancreas' system linking insulin delivery with continuous glucose monitoring (CGM), in adults with type 1 diabetes in a controlled setting.

Three randomised crossover studies compared closed-loop insulin delivery with conventional insulin pump therapy on two separate occasions, matched in meals and activities. During closed-loop visits, CGM values were entered into a computer containing a model predictive control algorithm which advised on basal insulin infusion for subcutaneous delivery, every 15 minutes. During control visits, usual insulin pump regimen was continued. The feasibility study evaluated overnight closed-loop in 12 adults (seven females, mean age 37.7 years, HbA1c 7.8%) following 60g-carbohydrate evening meal. A follow-up study assessed overnight closed-loop in 12 further adults (seven females, mean age 37.2 years, HbA1c 7.8%) following 100g-carbohydrate meal and (mean 564 ml) white wine. The third study evaluated 24 hours of closed-loop in 12 pregnant women (mean age 32.9 years, 19 to 23 weeks gestation, HbA1c 6.4%) during normal daily activities, including low and moderate intensity exercise. Activity and glucose levels were also measured during free-living. CGM performance during exercise was evaluated.

Overnight closed-loop insulin delivery in adults, compared with conventional pump therapy, increased time spent with plasma glucose in target range ($3.9 - 8.0$ mmol/l) following both standard meal (81% versus

57%; $p = 0.012$) and large meal accompanied by alcohol (70% versus 46%; $p = 0.012$). Glycaemic variability, and time spent in hypo- and hyperglycaemia were lowered. In pregnant women, day and night closed-loop insulin delivery was as effective as usual pump regimen (81% versus 81% time spent with plasma glucose $3.5 - 7.8$ mmol/l; $p = 0.754$). Hypoglycaemia occurred following exercise, although closed-loop prevented nocturnal episodes. Glycaemic control during free-living was suboptimal, compared with controlled diet and exercise conditions. Accuracy of CGM was lower during exercise.

In conclusion, these studies confirm the feasibility and efficacy of overnight closed-loop insulin delivery in adults with type 1 diabetes. Closed-loop is safe during pregnancy and may be beneficial in women with suboptimal glycaemic control. Meals and physical activity currently limit optimal daytime use of closed-loop.

# Contents

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# List of abbreviations

| | |
|---|---|
| ANOVA | Analysis of variance |
| AUC | Area under the curve |
| CHO | Carbohydrate |
| CL | Closed-loop |
| CV | Coefficient of variation |
| CGM | Continuous glucose monitoring |
| CSII | Continuous subcutaneous insulin infusion |
| DCCT | Diabetes Control and Complications Trial |
| JDRF | Juvenile Diabetes Research Foundation |
| HbA1c | Glycosylated haemoglobin |
| ISO | International Standards Organisation |
| IQR | Interquartile range |
| RAD | Relative absolute difference |
| MET | Metabolic equivalents |
| MPC | Model predictive control |
| MDI | Multiple daily injections |
| PAEE | Physical activity energy expenditure |
| PID | Proportional integral derivative |
| SMBG | Self-monitoring of blood glucose |
| SD | Standard deviation |
| YSI | Yellow Springs Instrument |

# Chapter 1

# Introduction

## 1.1 Glucose regulation

In health, multiple pancreatic and gastrointestinal hormones act to maintain glucose within a narrow range.[1] Circulating glucose is derived from two main sources: intestinal absorption during the fed state and hepatic metabolism during fasting. In the fasted state, glucagon produced by alpha cells in the pancreas facilitates glycogenolysis (the breakdown of glycogen or stored glucose) and gluconeogenesis (formation of glucose from lactate and amino acids), thus promoting appearance of glucose in the circulation. Following meal ingestion, the rise in glucose levels stimulates the secretion of insulin from pancreatic beta cells, resulting in glucose uptake into skeletal muscle and storage in the liver as glycogen, thus increasing disposal of circulating glucose. Amylin, which is co-secreted with insulin from beta cells, acts to delay gastric emptying and suppress appetite following a meal. Both amylin and insulin have an inhibitory effect on glucagon secretion. Cortisol, epinephrine and growth hormone, known as the counter-regulatory hormones, are released in response to low glucose levels.

## 1.2 Diabetes

### 1.2.1 Definition

Diabetes is a chronic condition characterised by elevated blood glucose levels, resulting from a lack of insulin production and/or an inability of the body to respond to insulin. The current World Health Organisation diagnostic criteria for diabetes are

fasting plasma glucose $\geq$ 7.0 mmol/l or two-hour plasma glucose $\geq$ 11.1 mmol/l.[2]

### 1.2.2 Types

There are two main forms of diabetes, type 1 and type 2, the latter accounting for up to 95% of cases. Type 1 diabetes is characterised by autoimmune destruction of insulin-secreting beta cells in genetically predisposed individuals, resulting in complete or near-complete loss of insulin production.[3] Type 2 diabetes is a combination of ineffective action of insulin, also known as insulin resistance, and progressive deterioration in beta cell function, resulting in inadequate insulin production.

### 1.2.3 Prevalence

The worldwide prevalence of diabetes (type 1 and 2) was 6.4% in 2010, affecting 285 million adults. This figure is projected to increase to 439 million by 2030, with the major escalation (69%) in developing nations and 20% in developed countries.[4] This increase, at a rate of 2.2% per year, is nearly twice the annual growth rate of the total world adult population. Data from the most recent UK National Health Service annual audit reported a prevalence of diagnosed diabetes in the UK of 4.35%, almost 10% (0.40%) of which are type 1 diabetes.[5]

### 1.2.4 Healthcare burden

Diabetes is associated with significant morbidity, resulting in a twofold increased risk of hospital admission, longer inpatient stays, and reduced life expectancy. The total global expenditure for diabetes in 2010 was estimated at US$376 - 672 billion, accounting for 12% of the world's total health budget.[6] There is a huge disparity between countries, with the USA spending 52.7% of global health expenditure on diabetes, and India, the nation with the highest diabetes population in the world, less than 1%. An estimated 10% of the National Health Service budget in the UK is spent on treatment of diabetes and its complications.[5]

## 1.3 Monitoring of diabetes

### 1.3.1 Conventional methods

Frequent glucose monitoring is imperative to maintaining target glucose levels. The American Diabetes Association recommends regular fingerprick capillary blood tests

Figure 1.1: FreeStyle Navigator continuous glucose monitor showing receiver and transmitter


at least three times daily to guide insulin timing and doses.[7] Drawbacks include the invasiveness, pain and inconvenience associated with the technique. In addition, fingerprick testing only provides a snapshot of glucose values with no information on glycaemic trends throughout the day. Accuracy of glucose measurement varies widely between devices, with inferior performance at glucose extremes.[8]

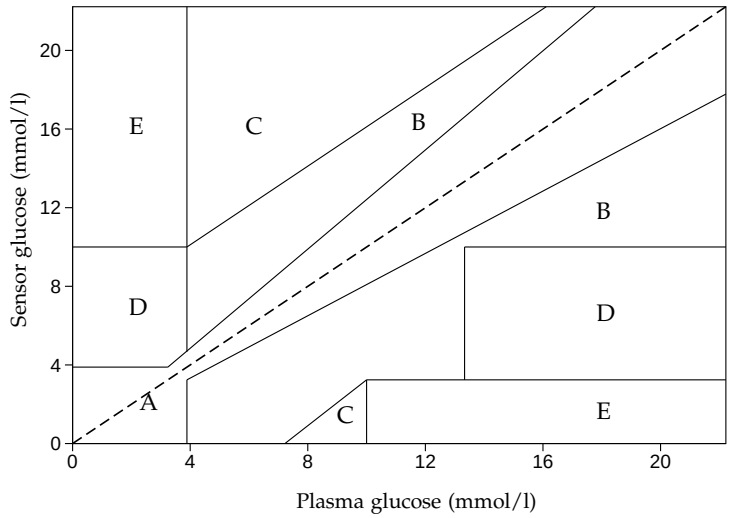
### 1.3.2 Continuous glucose monitoring

The original idea of continuous glucose monitoring (CGM) dates back to the 1960s. The earliest approaches used invasive intravascular access to determine glucose levels every second to 15 minutes, which is associated with a substantial risk of infection and thrombosis. In the last two decades, the focus has shifted towards the development of less invasive CGM devices which measure glucose in the interstitial fluid, and remains the most promising minimally invasive route for outpatient monitoring of glucose.[9] The components include a transcutaneous sensor connected to a transmitter, and linked wirelessly to a hand-held receiver (Figure 1.1). The receiver displays glucose values updated every one to five minutes, as well as directional arrows indicating glycaemic trends in real-time.

#### 1.3.2.1 Measuring accuracy

Various methods exist for evaluating the numerical and clinical accuracy of CGM devices. The Clarke error grid analysis, shown in Figure 1.2, uses a cartesian diagram to demonstrate the relationship between sensor (displayed on the $y$-axis) and reference (displayed on the $x$-axis) glucose measurements.[10] The diagonal represents perfect agreement of the two values, whilst points above and below the line indicate over-

Figure 1.2: Clarke error grid




**Notes:** Zones A to E represent varying levels of clinical accuracy. Adapted from [10]

and underestimation of reference glucose, respectively. The diagram is divided into five zones representing varying levels of accuracy: values in zone A and B are deemed clinically acceptable, whilst values in zones C, D or E are considered clinically unsafe. Zone A includes glucose values that deviate from reference by less than 20% or where both sensor and reference are in the hypoglycaemic range ($< 3.9$ mmol/l), while zone B represents those that deviate by more than 20% but are benign. Points in zone C may lead to unnecessary treatment of acceptable glucose values. Those in zone D indicate a potential failure to detect hypo- or hyperglycaemia, usually associated with rapidly changing glucose concentrations. Zone E represents erroneous sensor behaviour which may result in incorrect treatment.

The International Standards Organisation (ISO) 15197:2003 is the minimum acceptable standard for SMBG, and can also be applied to CGM devices. The criteria require that at least 95% of values lie within 0.8 mmol/l of the reference glucose when it is $\leq 4.2$ mmol/l, or within 20% when $> 4.2$ mmol/l.[11]

The relative absolute difference (RAD) is a commonly used measure, reflecting the numerical proximity of CGM readings with reference blood glucose values corresponding in time. Expressed as a percentage, RAD is calculated as:

$$\text{RAD} = \left| \frac{\text{Reference glucose} - \text{Sensor glucose}}{\text{Reference glucose}} \right| \times 100.$$

Bias measures the difference between paired CGM and reference glucose values, expressing both magnitude and direction of error. Positive bias indicates over-reading while negative bias indicates under-reading by the sensor.

#### 1.3.2.2 Development of CGM

In 1999, Medtronic developed the first commercially available continuous glucose sensor, known as CGMS Gold. A glucose oxidase enzyme-based electrode inserted directly into the subcutaneous tissue catalyses the oxidation of glucose and oxygen to hydrogen peroxide. Subsequent dissociation of hydrogen peroxide generates an electrical current, the magnitude of which is used to estimate the interstitial glucose concentration.[12] Evaluation of CGMS gave 95% of values in Zones A and B of the Clarke error grid analysis, and detected significantly more episodes of hypoglycaemia and postprandial hyperglycaemia compared with conventional SMBG.[13] Sensor failure rate was 28%, attributed to fluctuations in the electrical current signal from tissue reactions around the electrode.

The GlucoDay (Menarini, Florence, Italy) and the SCGM1 (Roche Diagnostics, Mannheim, Germany) sensor systems use the microdialysis technique where interstitial fluid is collected via a subcutaneously implanted semi-permeable dialysis fibre and transported to a flowcell located on the body surface containing a glucose oxidase sensor. Unlike the needle-based CGMS Gold (Medtronic, Northridge, CA, USA), external placement of the sensor requires longer tubing which, in combination with a low perfusion rate, introduces an additional transport lag. This delay is up to 35 minutes for the SCGM1, which has been withdrawn from clinical use.[14] The GlucoDay is approved for retrospective analysis. A newer generation microdialysis sensor, the GlucoMenDay (Menarini, Florence, Italy) reports improved sensor stability, minimised interferences and longer sensor life, with median RAD of 7.7% in euglycaemia and 9.6% in hypoglycaemia (Table 1.1).[15]

The GlucoWatch G2 Biographer (Cygnus, Redwood City, CA), a non-invasive device that uses reverse iontophoresis to measure interstitial glucose [19], was evaluated in a trial against the Guardian REAL-Time CGM (Medtronic, Northridge, CA, USA).[20] After 18 months, the decline in HbA1c in the GlucoWatch group was lower, and compliance was only 20% (versus 57% for Guardian REAL-Time). Difficulty with using the device and increased side effects such as skin irritation resulted in its with-

Table 1.1: Comparison of accuracy of commercially available CGM devices

| | Navigator[a] | DexCom STS[a] | DexCom SEVEN PLUS[b] | Guardian RT[a] | Enlite[c] | GlucoDay[a] | GlucoMenDay[d] |
|---|---|---|---|---|---|---|---|
| Mean relative absolute difference (%) | 15.3 | 21.2 | 16.8 | 15.2 | 13.9 | 15.6 | 10.4 |
| Median relative absolute difference (%) | 11.8 | 18.4 | 13.3 | 13.3 | — | 10.7 | 7.7 |
| Values within ISO requirements[e] (%) | 72.2 | 52.2 | 73.0 | 73.2 | — | 76.9 | 89.3 |
| Clarke error grid – zones $A + B$ (%) | 99.7 | 100 | 94.8 | 97.5 | 97.3 | 98.7 | 100 |
| Clarke error grid – zones $C + D + E$ (%) | 0.3 | 0.0 | 5.2 | 2.5 | 2.8 | 1.3 | 0.0 |

**Notes:** [a] Data from [16]; [b] Data from [17]; [c] Data from [18]; [d] Data from [15]; [e] CGM values within $\pm 0.8$ mmol/l when reference glucose $\leq 4.2$ mmol/l and within $\pm 20\%$ when $> 4.2$ mmol/l, based on ISO 15197:2003.

drawal from commercial use.

Accuracy of the DexCom STS (San Diego, CA, USA), Guardian REAL-Time (Medtronic, Northridge, CA, USA), FreeStyle Navigator (Abbott Diabetes Care, Alameda, CA, USA) and Glucoday (Menarini, Florence, Italy) was assessed during hypoglycaemic clamp studies.[16] Median RAD was 18.4%, 13.3%, 11.8% and 10.7% for each device, respectively (Table 1.1). The FreeStyle Navigator was more accurate during hypoglycaemia. The DexCom STS has since been superseded by the next generation device, DexCom SEVEN PLUS (San Diego, CA, USA), which has been shown to have higher accuracy with median RAD of 13.6%.[21] Similarly, the recently released Enlite sensor (Medtronic, Northridge, CA, USA) has a mean RAD of 13.9% (Table 1.1).[18]

Aside from the electrochemical sensors described above, there are several other approaches under development, employing a range of technologies including optical and electromagnetic methods, and varying in their degree of invasiveness.[22]

#### 1.3.2.3 Efficacy studies

One of the first randomised trials was carried out using CGMS Gold (Medtronic, Northridge, CA, USA) in 161 adults and children, demonstrating a reduction in HbA1c of 1% at three months when CGM was used continuously (but not with intermittent use), compared with conventional SMBG.[23]

The Juvenile Diabetes Research Foundation (JDRF) conducted a multicentre clinical trial comparing CGM with SMBG in 322 subjects with type 1 diabetes treated by multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII), over 26 weeks.[24] There was a significant improvement in HbA1c (0.53%) with CGM use amongst patients aged 25 years and older, but no difference in those under 25 years of age. Notably, compliance with CGM, defined as wearing the device for six days each week, was highest in subjects over 25 years (83%) compared with 30% amongst 15 to 24 year olds and 50% in 8 to 14 year olds. Older age, more frequent self-reported blood glucose measurements pre-study, and higher proportion of sensor glucose within target range ($3.9 - 10.0$ mmol/l) in the first month were associated with greater CGM use at six months.[25] Compliance with CGM was correlated with sustained improvement in HbA1c in all age groups. A meta-analysis of 19 randomised trials comparing CGM with SMBG showed a significant improvement in HbA1c in adults with type 1 (0.50%) and type 2 (0.70%) diabetes, with no difference in children.[26]

Although the JDRF multicentre trial was not powered to evaluate hypoglycaemia

outcomes, a reduction in the rate of severe hypoglycaemia was observed in those patients 25 years and older who continued to use CGM after the randomised phase of the trial from 21.8 events per 100 person-years to 7.1 events per 100 person-years six months later.[27] Another randomised trial in 120 children and adults with HbA1c $< 7.5\%$ on intensive insulin therapy for type 1 diabetes demonstrated a reduction in time spent below 3.5 mmol/l from 0.97 to 0.48 hours per day and prevention of severe hypoglycaemia with real-time CGM, without any deterioration in HbA1c after six months.[28]

Two months of CGM use in 16 MDI-treated patients with severe hypoglycaemia resulted in a reduction in frequency of hypoglycaemia, improved HYPO-scores (composite measure of severe hypoglycaemia episodes over the previous year and a four-week record of events below 3 mmol/l), and less fear of future hypoglycaemia.[29] Counter-regulatory responses to hypoglycaemia were evaluated in 11 adolescents with hypoglycaemia unawareness during hypoglycaemic clamp studies performed at baseline and four weeks after real-time CGM versus SMBG.[30] CGM resulted in an improvement in epinephrine responses as well as perceived adrenergic symptom scores.

Recent Cochrane review of 22 randomised trials in adults and children with type 1 diabetes concluded an added benefit on glycaemic control when CGM was used in combination with CSII, known as 'sensor-augmented' pump therapy: 0.7% reduction in HbA1c versus 0.2% for CGM alone.[31] In the STAR1 trial, 146 participants aged $12-72$ years already treated by CSII were randomised to either sensor-augmented pump therapy or standard pump with SMBG.[32] At 26 weeks there was no difference in HbA1c between the groups. However, subgroup analysis revealed that patients with 60% or greater compliance with sensor use had a significant improvement in HbA1c. The STAR3 study demonstrated a benefit of sensor-augmented pump therapy over MDI alone in 485 patients with type 1 diabetes: 0.8% versus 0.2% reduction in HbA1c at 12 months, respectively.[33] A higher proportion of patients in the pump group achieved the HbA1c target of $< 7\%$ (27% versus 10%), without any increase in severe hypoglycaemia. Amongst adults, baseline HbA1c $> 9.1\%$, age above 35 years and longer duration of diabetes ($> 18$ years) were strong predictors of benefit from sensor-augmented pump therapy.[34] The SWITCH study evaluated 153 adults and children with CSII-treated type 1 diabetes on sensor ON versus sensor OFF for six months each with a four month washout period, in a randomised crossover design.[35] HbA1c was 0.43% lower in the sensor ON group in both adults and children at six months, but reverted to pre-study levels on discontinuation of

sensor use.[36]

#### 1.3.2.4 Clinical utility

Uninterrupted glucose sensing over 24 hours has several advantages over conventional SMBG. According to a consensus guideline for the use of CGM, these include: [37]

1. Real-time information about rate and direction of glucose change including trends that could lead to hypo- or hyperglycaemia;
2. Tighter diabetes control; and
3. Better understanding of the impact of food, exercise, stress and other factors on glucose.

Although SMBG has superior point accuracy, it does not provide the necessary information to avoid excursions into hypoglycaemia or hyperglycaemia whilst glucose is still within normal range. CGM can be used for both diagnostic and therapeutic purposes, including optimising insulin regimens where tight glycaemic control is crucial, such as during pregnancy. Recent Endocrine Society clinical practice guidelines recommend real-time CGM use in children, adolescents and adults who are able to use the devices on a nearly daily basis.[38] Intermittent retrospective CGM use may be useful in assessing nocturnal hypoglycaemia, dawn phenomenon (morning hyperglycaemia), postprandial hyperglycaemia, changes in therapy and in patients with hypoglycaemic unawareness.

Widespread use of CGM has been limited by its relatively high cost in countries without healthcare reimbursement schemes. Real-time CGM use is covered by most healthcare plans in the USA. Some European countries, including the Netherlands, Israel and Sweden, have reimbursement schemes for patients with recurrent severe hypoglycaemia. But in the majority of other nations, CGM use is limited by high user costs: US$4380 per person compared with US$550 − 2740 for SMBG.[39] One cost-benefit analysis of CGM estimated US$100,000 for each quality adjusted life year gained.[40] In patients with an HbA1c $< 7\%$, CGM had a benefit on immediate quality of life and reduction in microvascular complications. No benefit was seen on long term glucose control or in patients with HbA1c $> 7\%$.

A quality of life survey of CGM users reported reduced fear of hypoglycaemia, decreased stress, and increased confidence with using CGM to make changes to insulin regimens.[41] Evidence from randomised trials indicates a benefit of CGM on

glycaemic control, but also highlights the importance of careful patient selection, which should take into consideration willingness to use the device. Reasons for stopping CGM include cost, bulkiness, adhesive problems and alarms.[41] Participants in the multicentre JDRF CGM trial reported alarms, body issues (insertion sites and size of device), and pain with insertion as the major barriers to CGM use.[42] In the same survey, the ability to see glucose trends was described as being the best aspect of CGM, with other benefits including ability to self-correct out of range glucose levels, the large amount of data available, and detection of hypoglycaemia. More frequent monitoring was associated with higher satisfaction amongst both adults and youth.

#### 1.3.2.5 Barriers to use

The main challenge of CGM devices is in improving their accuracy and reliability, especially in the hypoglycaemic range. Performance of the commercially available CGM devices may be affected by calibration errors, sensor artefacts, and physiological delays which include a $4-20$ minute lag of transport of glucose between blood and interstitial fluid compartments as well as a $5-15$ minute device-dependent delay associated with sensor signal processing and filtering out measurement noise. The time lag may be more pronounced when glucose levels are fluctuating or at extremes of the normal range, affecting accuracy of calibration of some CGM devices. A delay of 16.8 minutes during rapid glucose fall, compared with 11.7 minutes at steady glucose levels and 9.9 minutes during rising glucose was observed with the FreeStyle Navigator (Abbott Diabetes Care, Alameda, CA, USA).[43] Analysis of the DexCom SEVEN PLUS (San Diego, CA, USA) demonstrated lag times between 4.5 and 5.7 minutes, with no diminution in accuracy when calibrations were done during rapidly changing glucose.[21] Evaluation of the Enlite next generation sensor (Medtronic, Northridge, CA, USA) showed a time lag of 7.9 and 11.7 minutes for sensors placed in the abdominal and buttock regions, respectively.[18]

Inherent imprecision in the capillary blood glucose meter or glucose strips used for calibration can affect CGM accuracy. Calibration of the DexCom SEVEN PLUS (San Diego, CA, USA) with a laboratory standard YSI 2300 analyser reduced the median RAD from 13.6% to 5.0%.[21] This source of error is minimised in the FreeStyle Navigator which has a built-in blood glucose meter for calibrations. Accuracy of CGM may be lower overnight, which may be related to changes in subcutaneous blood flow and oxygen availability with lack of activity.[44]

Insertion of the sensor itself induces an inflammatory reaction with an increase

in metabolically active cells suggesting the glucose concentration in the immediate vicinity of the sensor is in more rapid equilibrium with blood than the rest of the interstitial fluid compartment. However over time this process results in encapsulation and protein aggregation around the sensor electrode with subsequent reduced glucose influx and progressive inactivation of glucose oxidase enzyme. These events, known as 'biofouling' or 'sensor drift', may explain the reduced performance towards the end of the life of each sensor (usually $3-7$ days). The microdialysis-based sensors, in comparison, appear to be resistant to such processes via continual release of perfusate into surrounding tissue which dilutes the proteins that stimulate the foreign body response and thus prevents fibrous capsule formation.[15]

All CGM devices have incorporated safety alarms for detecting low glucose which may be especially beneficial overnight. However, current sensors are limited by a high frequency of false alarms and limited audibility. A study in 20 children using CGM overnight demonstrated a false alarm rate of 55%, with subjects waking to only 29% of alarms.[45] False alarms increase patient anxiety and may lead to unnecessary treatment of hypoglycaemia or overcorrection of hyperglycaemia due to the time lag of sensor glucose. At the same time sensor alarms must be robust enough to awaken patients at night, considering the blunted response to hypoglycaemia that occurs with type 1 diabetes as well as the reduced auditory response during sleep. Severe hypoglycaemia has been shown to be present for up to four hours before a seizure occurs, hence sensor detection algorithms that incorporate duration of hypoglycaemia may reduce false positive alarms and thus be more clinically acceptable.[46]

## 1.4 Treatment of diabetes

### 1.4.1 Glucose targets

The ultimate goal of insulin therapy is maintenance of adequate glycaemic control whilst minimising the risk of hypoglycaemia. Optimising glycaemic control early in the disease may be crucial to reducing the risk of diabetes-related complications. This may be explained by the 'metabolic memory', where early derangements in glycaemic control are remembered in target organs.[47] Dynamic fluctuation in blood glucose, known as glycaemic variability, is an independent predictor of worse outcomes.[48] Chronic hyperglycaemia can induce oxidative stress, resulting in vascular damage.[49] Recurrent episodes of hypoglycaemia may also have a negative effect on cardiovascular outcomes via reactive increase in counter-regulatory hormones

including catecholamines that can induce vasoconstriction and platelet aggregation, and augment the risk of cardiac arrhythmias.

Intensive therapy is known to prevent or delay both the microvascular (retinopathy, neuropathy and nephropathy) and macrovascular (coronary and peripheral vascular disease) complications of type 1 diabetes.[50; 51; 52; 53] The American Diabetes Association recommends aiming for an HbA1c as low as can be achieved safely and generally below 7%.[7] The 2010 UK National Health Service audit showed that 17% of patients with type 1 diabetes had an HbA1c above 10%, with only 28% achieving target HbA1c $\leq$ 7.5% as recommended by the National Institute for Health and Clinical Excellence.[5]

Intensive insulin therapy however has been linked with weight gain, with associated high blood pressure and adverse cholesterol profiles.[54] Tailoring of insulin regimes to achieve glycaemic targets can be challenging due to inter-subject variability in insulin requirements. In addition, insulin sensitivity within the same individual fluctuates with time of day, stress levels, physical activity, concurrent illness and meals consumed.

### 1.4.2 Current therapies

#### 1.4.2.1 Multiple daily injections (MDI)

Patients with type 1 diabetes are dependent on lifelong insulin replacement, administered into the subcutaneous tissue either by MDI or CSII. MDI therapy is the more widely available treatment regimen, necessitating administration of a combination of longer-acting and rapid-acting (prandial) insulin injections. A significant proportion of patients fail to achieve optimal diabetes control on MDI, predominantly due to high glucose variability.

#### 1.4.2.2 Continuous subcutaneous insulin infusion (CSII)

Insulin pumps, which deliver rapid-acting insulin in a continuous fashion, have overcome many of the limitations associated with MDI.[55] They mimic more closely the pattern of insulin secretion by the pancreas, thus allowing greater lifestyle flexibility. CSII technology has advanced rapidly since first introduced over 30 years ago. The newer models have several advanced features including the incorporation of alarms, bolus calculation wizards and the ability to adjust basal rates with fine precision.

More recently, 'patch pumps' are being developed. The first of these to be com-

mercially available is the Omnipod Insulin Management System (Insulet Corp, Bedford, MA, USA). Their main advantage is a 'tube-free' system as the infusion cannula is integrated into the pump which attaches to the body with an adhesive patch, hence overcoming risks of obstruction or detachment of tubing. Patch pumps are slimmer and more discreet, but limitations include a smaller insulin reservoir, adhesive intolerance and high cost of single-use consumables.[56]

A review of all CSII studies by the National Institute for Health and Clinical Excellence in 2010 concluded that CSII therapy in both children and adults resulted in improved glycaemic control as reflected by a reduction in HbA1c, with the magnitude of decrease correlated with higher HbA1c at baseline, and fewer hypoglycaemic events.[57] Overall quality of life was improved and there was no increase in diabetic ketoacidosis. A meta-analysis of 22 studies found a 4.2-fold lower rate of severe hypoglycaemia during CSII compared with MDI, with the greatest reduction in those with highest rates at baseline and those with longest duration of diabetes.[58] Importantly, glycaemic control was not compromised by the reduction in hypoglycaemia during CSII, with an improvement in HbA1c of 0.62%. Twenty adults with repeated non-severe (> four events/week) and severe (> two events in two years) hypoglycaemia were evaluated in a pilot study, demonstrating a significant decrease in episodes of hypoglycaemia and improvement in hypoglycaemic awareness after 24 months of CSII therapy, with no change in HbA1c.[59]

There is considerable variation in the frequency of pump usage worldwide, predominantly related to allocation of healthcare funding, ranging from over 25% in the USA to less than 4% in the UK.[60] Within Europe, pump usage varies from 20% in Norway and Austria to less than 2% in Portugal and Russia.[61] The pump itself, assuming a four-year life, costs £430 – £720 annually, and consumables are estimated at £1,800 – £2,000 per year. Compared with MDI, CSII costs an extra £1,700 per annum.[57] The National Institute for Health and Clinical Excellence published a guidance on CSII in 2008, reporting an incremental cost-effectiveness ratio ranging from £24,720 – £37,712 per quality-adjusted life year gained with CSII compared with MDI, dependent on baseline HbA1c.[62]

#### 1.4.2.3 Immunomodulatory therapy

Pancreas transplantation is considered the gold standard endocrine replacement therapy, and is associated with improved quality of life and reversal of hypoglycaemia unawareness.[63] However, major drawbacks are the potential morbidity and mor-

tality associated with major surgery, and side-effects from long term immunosuppression including deterioration in renal function. Graft survival rates vary from 16% for pancreas transplants alone to 36% for simultaneous pancreas and kidney transplants. Islet cell transplantation is less invasive, involving placement of transplanted cells into the portal vein thus enabling instantaneous glucose detection and direct insulin secretion. Following the introduction of the Edmonton steroid-free immunosuppression protocol, early outcomes of islet cell transplantation appeared promising.[64] However only 10% of patients remained insulin-independent after five years.[65] Limited availability and viability of islet cells remain major hurdles. Research into alternative sources, such as tissue stem cells and xenografts, is ongoing.

Another approach is the use of immunomodulatory agents in preventing or treating the autoimmune destruction of beta cells pathognomonic of type 1 diabetes.[66] Several therapies have been proposed but none have yet received regulatory approval.

### 1.4.3 Insulin delivery

#### 1.4.3.1 Subcutaneous route

Insulin absorption from subcutaneous tissue is influenced by factors including those related to insulin preparation (e.g. dose, concentration, type), and local tissue blood flow (e.g. anatomical site of injection, injection depth, lipodystrophy, age, temperature, exercise). The high variability of insulin absorption can be attributed to a combination of one or more of these factors. Intra-individual coefficient of variation of insulin absorption of regular insulin from a single anatomical site under controlled conditions is reported to range from $15-25\%$, whilst inter-individual variability is at least 10% higher.[67] Less concentrated insulin (U40 versus standard U100 insulin), higher temperatures and a lower proportion of subcutaneous fat are associated with enhanced insulin absorption.[68]

Insertion of a CSII infusion catheter results in trauma to subcutaneous tissue, generating an inflammatory response which may increase capillary permeability and hence affect absorption of insulin. A study in healthy volunteers demonstrated maximal local tissue blood flow two days after catheter insertion, with a return to baseline at 4 days.[69] Although the rate of insulin absorption increased with catheter weartime, there was no significant change in peak plasma insulin concentration or total amount of insulin absorbed. Euglycaemic clamp studies were performed in adolescents with type 1 diabetes on day one and four of insulin catheter wear.[70] Boluses of rapid acting insulin resulted in an earlier peak and shorter duration of action with

longer catheter wear but overall insulin concentration was unchanged.

#### 1.4.3.2 Novel approaches

Formation of insulin hexamers that impede absorption from the subcutaneous depot contribute to the delays in subcutaneous insulin delivery. Potential solutions include improving delivery and/or the molecule itself.

The challenge is to develop a form of insulin that is stable enough to be stored and will not form amyloid fibrils in suboptimal conditions, whilst still being able to rapidly break down from the hexameric form into monomers that can then enter the bloodstream. There are at least two new insulin formulations under development. VIAject (Biodel, Danbury, CT, USA) is a recombinant human insulin formulation which, on subcutaneous injection, retains insulin in its monomeric form resulting in a faster onset of action compared with the rapid acting insulin analogues.[71] Addition of EDTA which pulls zinc away from the insulin molecules and citric acid which masks the charges on the molecule surface together stimulate increased dissociation of insulin hexamers. Recombinant human hyaluronidase (rHuPH20) is a genetically engineered version of the enzyme hyaluronidase which cleaves hyaluronan polymers that normally block fluid movement in the interstitium. Bulk fluid flow is hence increased, facilitating the presentation of injected drugs to blood vessels. Co-administration of rHuPH20 (Halozyme Therapeutics, San Diego, CA, USA) with lispro or regular human insulin at meal times in patients with type 1 diabetes resulted in faster onset and higher peak plasma insulin concentrations, with subsequent improved postprandial glycaemic control.[72] Tolerability over the long term is yet to be determined.

Increase in temperature at the site of insulin delivery may increase insulin absorption.[68] The InsuPatch (InsuLine, Israel) is a local skin heating device that warms the site of subcutaneous insulin infusion. Concurrent use with prandial insulin boluses in 17 CSII-treated adults demonstrated a faster and greater rise in insulin concentrations with resulting reduction in postprandial glucose excursions.[73]

Another approach to overcome the delay in insulin action is to reduce the rate of appearance of meal-related glucose. Pramlintide, the synthetic analogue of the hormone amylin, acts to slow gastric emptying and secretion of digestive enzymes in addition to inhibiting release of glucagon and modulating appetite. Co-administration of pramlintide with insulin at mealtimes may reduce postprandial hyperglycaemia.[74]

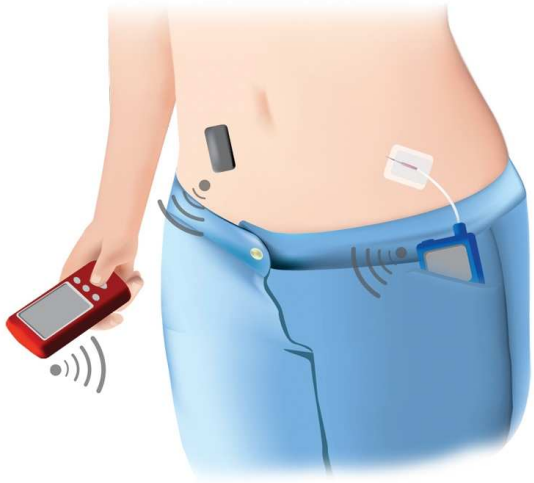
#### 1.4.3.3 Alternative routes

The intraperitoneal route more closely mimics physiologic insulin secretion with most of the insulin delivered directly to the portal circulation, achieving maximal action within 15 minutes and lower circulating insulin levels. Catheter implantation requires a surgical procedure which carries an associated risk of infection, fluid accumulation and skin thickening. In the long term, occlusion due to insulin aggregation may result in insulin under-delivery. Evaluation of the Diaport (Roche Diagnostics, Mannheim, Germany) system in 60 patients demonstrated a reduction in severe hypoglycaemia but an increased rate of treatment-related complications, compared with conventional CSII.[75] An observational study of 40 implanted pumps in subjects with type 1 diabetes reported 40 insulin under-delivery events in 24 pumps: 36 due to formation of insulin aggregates, and four due to catheter obstruction from peritoneal tissue overgrowth. Three pumps were removed prematurely, one because of electronic failure and two due to infection.[76]

The inhaled route for insulin delivery has had limited success thus far, with previous formulations being withdrawn from clinical use for reasons including lower bioavailability, irritation of airways, and variable effect in smokers or patients with lung disease. Afrezza (Technosphere, MannKind Corp, USA), an ultra rapid insulin administered via pre-metered inhaler, has a more rapid onset and shorter duration of action than subcutaneous insulin.[77] The active agent is Technosphere insulin, a dry powder insulin deposited as insulin monomers, resulting in peak insulin levels within $12 - 14$ minutes. When delivered at the start of a meal in patients with type 2 diabetes, Afrezza resulted in lower postprandial glucose excursions and lower rates of hypoglycaemia, with lesser or no weight gain compared with rapid acting subcutaneous insulin.[78]

Intradermal delivery of insulin has also been evaluated. Compared with subcutaneous administration (8mm needle), premeal intradermal injection of regular human insulin using a 1.5mm steel microneedle lowered postprandial glucose levels, although no difference was seen when lispro rapid acting insulin analogue was used.[79] Intradermal insulin resulted in faster uptake, higher maximum concentration and shorter systemic circulating levels of insulin.

Figure 1.3: Artificial pancreas (closed-loop) system



**Notes:** Illustration of artificial pancreas comprising continuous glucose monitor (black transmitter on abdomen), subcutaneous insulin pump (in pocket, connected via infusion set to abdomen), and hand-held device containing the control algorithm.

## 1.5 Closed-loop insulin delivery

### 1.5.1 Components

Recently, there has been increasing interest in developing an 'artificial pancreas' or closed-loop insulin delivery system that best mimics the human beta cell, aiming to safely achieve and maintain near normal glucose levels.[80] The artificial pancreas is composed of three components: a continuous glucose sensor (discussed in Section 1.3.2), a subcutaneous insulin pump or CSII (discussed in Section 1.4.2), and a control algorithm which computes the amount of insulin to be delivered by the pump based on real-time CGM measurements (Figure 1.3).

### 1.5.2 Control algorithm

There are two main groups of control algorithm used in artificial pancreas prototypes: model predictive control (MPC) and proportional integral derivative (PID). Fuzzy logic control is another algorithmic approach, which uses approximate reasoning to replicate conventional insulin dosing instructions by diabetes practitioners based on clinical judgement and medical knowledge.

#### 1.5.2.1 Model predictive control

The MPC algorithm links insulin delivery and meal ingestion to glucose excursions in a mathematical model.[81] This can involve a physiological model representing fundamental glucoregulatory processes, or a 'black-box' model disregarding the physiological insights but learning the insulin-glucose relationships using pattern recognition techniques. This information enables the construction of insulin infusion rates leading to a predefined 'target' glucose excursion. The insulin to be infused is obtained by minimising the difference between the model-predicted glucose concentration and the target glucose, over a prediction window corresponding to the duration of insulin action. A moving target range allows gradual normalisation of elevated glucose and faster normalisation of low glucose values.

MPC has the ability to 'learn' usual timing and content of meals and exercise patterns, enabling patient-personalised models to optimise future insulin delivery and reduce glycaemic variability. It is an adaptive system, whereby current glucose measurements are used to update model parameters such as insulin sensitivity, based on previous insulin infusion rates and glucose intake, in real-time. Prediction capabilities make MPC a suitable approach to compensate for time delays associated with subcutaneous glucose sensing and insulin delivery.

#### 1.5.2.2 Proportional integral derivative control

The PID algorithm, used widely in control systems in industrial settings, calculates insulin delivery based on three terms.[82] The proportional term adjusts insulin delivery in response to current glucose levels. The integral component adjusts insulin according to the area under the curve between measured and target glucose. The derivative term delivers insulin in response to the rate of change of blood glucose over time. Total insulin delivery is the sum of all three components, balanced by three constants, which are set individually. Unlike MPC which is proactive and has the ability to anticipate future glucose excursions related to the effect of administered insulin, meals and physical activity, PID is purely reactive to changes in blood glucose.

A variation on PID control, which replaces the integral component with a 'fading memory' where more recent glucose levels have a higher weighting than older values, has been evaluated.[83; 84] Addition of insulin feedback has been proposed to improve the ability of PID to accommodate delays in insulin absorption.[85]

### 1.5.3 Historical overview

In 1964, Kadish proposed and tested a closed-loop system based on an on-off control algorithm, using continuous glucose sensing with intravenous glucose and insulin infusions.[86] Albisser et al [87] and Pfeiffer et al [88] developed the first true 'artificial endocrine pancreas' system. The first commercial device, the Biostator, was introduced in 1977.[89] It operates as a fully closed-loop system using the intravenous-intravenous route, with infusion of insulin when glucose levels are elevated and dextrose when glucose levels are below target. Glucose is measured from whole blood via a glucose oxidase sensor in real-time. Biostator was initially developed to treat acute metabolic derangements such as diabetic ketoacidosis, but has since been used for research purposes. Limitations of this prototype system include the lack of portability, simplified algorithms, wastage of venous blood after each glucose measurement, and an increased risk of infection or thrombosis.

In 2000, a consortium of academic, clinical and industrial partners commenced work on the Advanced Insulin Infusion using a Control Loop project.[90] This involved stepwise simulation and clinical testing of a system using an intravenous glucose sensor (with a 30-minute time lag to simulate the delays associated with subcutaneous sampling), a control algorithm operated via a handheld computer, and a subcutaneous insulin pump. Clinical testing in 11 subjects with type 1 diabetes demonstrated 84% of glucose readings in the $3.5 - 9.5$ mmol/l range.

In 2003, Medtronic developed an 'external physiologic insulin delivery' system using CGMS Gold (Medtronic, Northridge, CA, USA), a PID controller and the Medtronic 511 Paradigm insulin pump, which was evaluated in ten patients with type 1 diabetes.[91] Glucose levels were within $3.9 - 10.0$ mmol/l for 75% of the time during closed-loop, compared with 63% during standard CSII with SMBG at home. There was no difference in episodes of hypoglycaemia. Roche developed a subcutaneous-subcutaneous closed-loop system with meal announcement utilising an empirical algorithm to determine insulin delivery based on SCGM1 (Roche Diagnostics, Mannheim, Germany) and operator input of meal carbohydrates.[92] Compared with standard multiple daily injections, 32 hours of closed-loop control reduced the frequency and quantity of carbohydrates required to treat hypoglycaemia in 12 subjects with type 1 diabetes.

### 1.5.4 Measuring performance

A number of metrics may be used to assess efficacy of closed-loop glucose control during clinical testing. The most widely used measure is 'proportion of time spent with glucose in target range'.[93] This range may vary according to the patient group under evaluation, with tighter targets required during pregnancy for example, to avoid hyperglycaemia-related adverse obstetric outcomes.[94] A target range of $3.9 - 8.0$ mmol/l is generally used for fasting and overnight, with $3.9 - 10.0$ mmol/l for postprandial conditions, consistent with American Diabetes Association guidelines.[95] Clinicians may be more familiar with mean glucose as a measure of glycaemic control. Glycaemic variability may be expressed in various ways including standard deviation of glucose, mean amplitude of glycaemic excursions and interquartile range.[96] The blood glucose rate of change can be used to measure the degree of fluctuation in glucose concentration. Time spent below target and frequency of episodes of hypoglycaemia are important safety measures. The low blood glucose index provides a composite measure of duration and extent of hypoglycaemia.[97] Time spent above target and the high blood glucose index can be used to quantify hyperglycaemia.

Optimal evaluation of closed-loop glycaemic control entails frequent measurement of whole blood or plasma glucose samples using a laboratory gold standard such as a YSI 2300 analyser. This is feasible for hospital-based studies, but is not practical for outpatient-testing of closed-loop insulin delivery. Glycosylated haemoglobin (HbA1c), the most widely recognised gauge of treatment outcomes, reflects glucose levels over the preceding six to eight weeks. Use of HbA1c as a marker of glucose control gives limited information and is restricted to studies performed over a longer duration. Sensor glucose is likely to be the most feasible method for evaluating closed-loop performance, but adjustment for inherent device inaccuracy may be required when interpreting the results.[98]

### 1.5.5 Body access routes

The Biostator established feasibility of closed-loop glucose control, but the intravenous route for glucose sensing and insulin delivery limit its use to research and inpatient settings. Intraperitoneal insulin delivery has similar drawbacks. Given the limitations of such invasive approaches, the subcutaneous route for both glucose sensing and insulin delivery is the most viable approach for outpatient application of closed-loop.

### 1.5.6 Clinical testing

Approaches to closed-loop insulin delivery differ by degree of user input, timing of application, or hormones infused as summarised in Table 1.2.[80]

#### 1.5.6.1 Low glucose suspend and pump shut-off

Suspension of insulin delivery during hypoglycaemia is the most straightforward application of an early first generation closed-loop system. The Paradigm Veo pump (Medtronic, Northridge, CA, USA), approved for commercial use in Europe since 2009 but awaiting USA Food and Drug Administration authorisation, can be linked with the Guardian REAL-Time or Enlite sensor (Medtronic, Northridge, CA, USA). Insulin delivery is suspended for up to two hours if the hypoglycaemia alarm is not responded to when sensor glucose falls below a predefined threshold. Data from 935 users showed 82% compliance with using the 'low glucose suspend' feature.[114] The majority of suspensions occurred in the late afternoon, with 45% lasting less than five minutes and 11% greater than 115 minutes. A user evaluation study in 31 adults showed that the low glucose suspend feature was activated 166 times (1.9 times per patient per week), with 76% occurring in the daytime.[99] Nocturnal hypoglycaemia ($\leq$ 2.2 mmol/l) was reduced from 46.2 to 1.8 minutes per day in those with highest baseline risk. Significant hyperglycaemia did not occur, with median glucose rising from 3.9 mmol/l to 8.2 mmol/l two hours after suspension of insulin delivery.

Assessment of low glucose suspend in children demonstrated reduction of time spent in hypoglycaemia from 101 minutes to 58 minutes per day.[100] Almost 25% of pump suspension events lasted the maximum two hours, with the majority occurring overnight. The efficacy of low glucose suspend was evaluated in a recent inpatient crossover study in 50 adults with type 1 diabetes, demonstrating reduction in the duration (138 minutes versus 170 minutes) and severity of exercise-induced hypoglycaemia (nadir plasma glucose 3.3 mmol/l versus 3.2 mmol/l), compared with not using the feature.[115]

Pump shut-off during the daytime using two different hypoglycaemia prediction algorithms was evaluated in 22 adult and young patients.[102] Using a pump shut-off time of 90 minutes and a threshold of 4.4 mmol/l, hypoglycaemia was prevented on 60% of occasions using a statistical algorithm, and 75% using a linear algorithm. A combination of up to five hypoglycaemia prediction algorithms was evaluated overnight, using a threshold of 4.4 mmol/l with a 35-minute prediction horizon.[101] Hypoglycaemia ($<$ 3.3 mmol/l) was prevented on 60% of nights when

## 1.5. CLOSED-LOOP INSULIN DELIVERY

Table 1.2: Closed-loop approaches

| Approach | Study population ($n$ = number of subjects) | Clinical studies | References |
|---|---|---|---|
| Low glucose suspend | Adults ($n = 31$) | User evaluation of Paradigm Veo pump + Guardian REAL-Time sensor[a] | [99] |
| | $1 - 18$ years ($n = 21$) | User evaluation of Paradigm Veo pump + Guardian REAL-Time sensor[a] | [100] |
| | $12 - 39$ years ($n = 26$) | Overnight pump shut-off during hypoglycaemia using prediction algorithms | [101] |
| | $6 - 38$ years ($n = 22$) | Daytime pump shut-off during hypoglycaemia using prediction algorithms | [102] |
| Overnight closed-loop | $18 - 65$ years ($n = 24$) | $13 - 14$ hours closed-loop versus open loop (control); randomised | [103] |
| | $5 - 18$ years ($n = 19$) | 12 hours closed-loop versus open loop (control); randomised | [104] |
| | Adults ($n = 20$) | 15 hours fully closed-loop versus open loop (control) | [105] |
| | $5 - 13$ years ($n = 8$) | $11 - 14$ hours fully automated closed-loop | [106] |
| Closed-loop with meal announcement | $12 - 18$ years ($n = 12$) | 36 hours closed-loop (+ manual bolus) versus open loop (control); randomised | [107] |
| | Pregnancy ($n = 10$) | 22 hours closed-loop (+ manual bolus) in early versus late gestation | [108] |
| | Pregnancy ($n = 12$) | 22 hours closed-loop (+ manual bolus) versus open loop (control); randomised | [109] |
| Closed-loop without meal announcement | $22 - 60$ years ($n = 8$) | 30 hours closed-loop (+ manual priming bolus) versus home open loop | [85] |
| | $19 - 30$ years ($n = 7$) | $8 - 24$ hours fully closed-loop versus home open loop | [110] |
| | $13 - 20$ years ($n = 17$) | 34 hours semi (+ manual priming bolus) versus fully closed-loop; randomised | [111] |
| | Adults ($n = 10$) | 29 hours fully closed loop versus home open loop | [91] |
| Bi-hormonal (insulin + glucagon) closed-loop | $19 - 71$ years ($n = 11$) | 27 hours bi-hormonal fully closed-loop | [112] |
| | Adults ($n = 7$) | 28 hours bi-hormonal (+ manual priming bolus) versus insulin only (control) closed-loop | [83] |
| | Adults ($n = 14$) | 33 hours bi-hormonal (+ manual priming bolus) comparing two closed-loop algorithms | [84] |
| Closed-loop with intra-peritoneal insulin delivery | Adults ($n = 8$) | 48 hours closed-loop (+ manual priming bolus) versus open loop (control); randomised | [113] |

**Notes:** [a]Medtronic, Northridge, CA, USA. System available in Europe for commercial use.

three algorithms were used to predict pump suspension, and on 75% of nights when two algorithms were used.

The main safety concern with interruption of insulin delivery, which may occur under normal closed-loop control, is the risk of hyperglycaemia and associated metabolic ketacidosis due to the short duration of action of rapid acting insulin analogues.[116] There were seven episodes of mild ketoacidosis in the two pump shut-off studies, none of which were associated with symptoms or clinical sequelae.[101; 102] Insulin suspension for up to 240 minutes during closed-loop studies using MPC in seven children resulted in a peak glucose of 11.6 mmol/l with no metabolic derangement.[117] Similarly, during closed-loop studies employing PID control in 17 children over 34 hours, there were 18 occurrences of insulin suspension for at least 60 minutes with no occurrence of significant hyperglycaemia or ketoacidosis.[118]

#### 1.5.6.2 Overnight closed-loop

Nocturnal hypoglycaemia is common; in the landmark Diabetes Control and Complications Trial (DCCT) 55% of severe hypoglycaemia episodes occurred during sleep.[119] Overnight closed-loop was evaluated in 17 subjects aged $5-18$ years with type 1 diabetes in three randomised crossover studies, including evaluation after slowly and rapidly absorbed large evening meals, and following moderate intensity evening exercise.[104; 120] Compared with conventional pump therapy, closed-loop in children increased time in target glucose ($3.9-8.0$ mmol/l) from 40% to 60%, and halved the time spent in hypoglycaemia ($< 3.9$ mmol/l) from 4% to 2%. There were no rescue carbohydrates administered during any of the 33 closed-loop nights.

Overnight closed-loop was tested in 20 adults in a non-randomised multicentre trial using an MPC controller developed *in silico*.[105] Time in target glucose ($3.9-7.8$ mmol/l) increased from 64% to 78%, and hypoglycaemia episodes ($< 3.9$ mmol/l) were reduced from 23 to five, compared with conventional pump treatment. A prototype fully automated closed-loop system was evaluated overnight in eight young children.[106] Time spent in target glucose ($3.9-8.0$ mmol/l) was 51%, with no differences in glycaemic control when closed-loop was initiated at 18:00 versus 21:00, and no episodes of treated hypoglycaemia.

#### 1.5.6.3 Closed-loop with meal announcement

Insulin dosing following meal consumption presents a major challenge to closed-loop glucose control. The fully closed-loop will ultimately operate autonomously delivering insulin in response to detected glucose levels. However, delays in insulin absorption complicate timely insulin delivery in response to rising glucose levels. Insulin overdosing may result in insulin 'stacking' and late postprandial hypoglycaemia. In the semi closed-loop approach, information on size and timing of meals is provided to the algorithm and prandial insulin is calculated and administered manually, with fully closed-loop control at other times.

Twelve adolescents were evaluated in a randomised crossover study using MPC-driven closed-loop over 36 hours, mimicking a typical day at school.[107] Compared with conventional pump therapy, closed-loop improved overall time in target glucose ($3.9 - 10.0$ mmol/l) from 49% to 84%, with 100% time in target overnight. Daytime hypoglycaemia associated with exercise and postprandial periods occurred during both interventions, although closed-loop prevented nocturnal episodes. Evaluation of closed-loop with meal announcement over 22 hours in ten women with type 1 diabetes during pregnancy demonstrated feasibility and safety in early and late gestation with no occurrence of hypoglycaemia.[108]

#### 1.5.6.4 Closed-loop without meal announcement

Feasibility of fully-closed-loop was first evaluated using a PID algorithm over 29 hours in 10 adults showing 75% time in target ($3.9 - 10.0$ mmol/l), compared with 63% during 'open loop' at home.[91] A 'hybrid' closed-loop system was tested in 17 children using a PID algorithm with manual administration of a priming ($25 - 50$% of the total) bolus $10 - 15$ minutes before each meal. Compared with fully automated closed-loop, semi closed-loop resulted in lower mean (7.8 mmol/l versus 8.3 mmol/l) and postprandial peak (10.8 mmol/l versus 12.6 mmol/l) glucose levels.[111] This approach was evaluated in eight adults using PID control with insulin feedback over 30 hours, with a manual insulin bolus of 2U delivered at the start of each meal.[85] Although satisfactory mean postprandial glucose levels were achieved ($< 10$ mmol/l), hypoglycaemia was not eliminated and supplemental carbohydrates were administered on eight occasions.

Administration of pramlintide prior to meals is being evaluated in a closed-loop system using PID control with insulin feedback over 24 hours.[121] Preliminary results showed a delayed time to (2.5 hours versus 1.5 hours) and reduced magnitude

of (4.9 mmol/l versus 6.3 mmol/l) peak glucose following lunch and dinner with the addition of pramlintide, compared with closed-loop insulin delivery alone.

A feasibility study employing fuzzy logic control in a fully closed-loop system (MD-Logic Artificial Pancreas system) in seven adults with type 1 diabetes over eight (12 occasions) or 24 hours (two occasions) demonstrated 73% of sensor values between $3.9 - 10.0$ mmol/l with no symptomatic hypoglycaemia.[110] Further validation of this approach is forthcoming.

#### 1.5.6.5 Dual hormone closed-loop

Glucagon may reduce the risk of hypoglycaemia more effectively than discontinuation of insulin delivery in a closed-loop system, due to its faster onset of action compared with the offset of insulin action.[122] The glucagon response to low glucose levels is gradually lost in type 1 diabetes. Co-administration of glucagon as part of a closed-loop system was evaluated in 11 adults during 24 hours of fully closed-loop control using an adaptive MPC algorithm.[112] Six subjects achieved mean blood glucose of 7.8 mmol/l with no hypoglycaemic events. Five subjects experienced hypoglycaemia requiring treatment, attributed to slower insulin absorption (time to peak plasma insulin 117 minutes versus 64 minutes for the other six subjects). Subsequent adjustment of the algorithm's insulin pharmacokinetic parameters averted further hypoglycaemia, although at a cost of a higher mean glucose of 9.1 mmol/l.

Dual glucagon and insulin delivery was evaluated in 11 subjects in a semi closed-loop system under fading memory proportional derivative control with manual delivery of $50 - 75\%$ of the bolus pre-meals, demonstrating 63% lower time spent in hypoglycaemia compared with insulin alone.[83] Compared with low gain, glucagon delivered using high gain parameters (pulses over five to ten minutes followed by a 50-minute off period) reduced frequency of hypoglycaemia even further. There was only one report of nausea and vomiting, during a low gain study. Of note, much lower doses of glucagon ($0.05 - 0.1$mg) were delivered by closed-loop at any one time, compared with the 1mg dose used as emergency treatment for hypoglycaemia. Limitations of glucagon use include its instability and tendency to form amyloid fibrils in solution, which may be reduced by use of an alkaline preparation. Another drawback is the depletion of liver glycogen stores with repeated administration, which may limit the ability of glucagon to prevent hypoglycaemia in a closed-loop system.[122]

#### 1.5.6.6 Closed-loop intraperitoneal insulin delivery

The major limitations of the subcutaneous-subcutaneous approach are the delays in insulin delivery and glucose sensing. A closed-loop system combining an implantable intraperitoneal pump with intravenous CGM placed in the superior vena cava was tested in four patients: sensor failure occurred in one subject, and glucose levels were maintained between $4.4 - 13.3$ mmol/l in the remaining three for 84% of the time.[123] Closed-loop intraperitoneal insulin delivery using PID control and subcutaneous glucose sensing was evaluated in a randomised study over two days in eight adults.[113] Excluding the early postprandial periods, closed-loop improved time spent in the $4.4 - 6.6$ mmol/l range (46% versus 29%) and lowered mean glucose (6.9 mmol/l versus 7.9 mmol/l) with no difference in time spent hypoglycaemic, compared with conventional CSII.

#### 1.5.6.7 Simulators

Compared with clinical studies, which are time consuming and costly to perform, computer-based simulated studies enable rapid systems evaluation without requirement for ethical or regulatory approvals.[124] Simulators enable evaluation of the effect of various parameters or scenarios that may be encountered in real life such as sensor errors, pump occlusion, hypoglycaemic episodes, exercise, errors in carbohydrate estimation and unannounced meals. In 2008, the USA Food and Drug Administration approved an *in silico* simulation environment as an alternative to animal trials for pre-clinical closed-loop studies.[125]

## 1.6 Thesis outline

In this thesis, I present the first randomised controlled closed-loop studies in adults and pregnant women with type 1 diabetes.

Chapter 2 describes a pilot study in 12 adults with type 1 diabetes evaluating the feasibility of overnight closed-loop insulin delivery. Subjects attended a clinical research facility for two overnight stays - on one night, closed-loop was commenced at 19:00 following a standard evening meal (60g carbohydrate) and continued until 08:00 the following morning; on the other night subjects remained on their usual insulin pump regimen overnight.

Chapter 3 describes a follow-up study in twelve new adults. Following on from the feasibility study, I wanted to evaluate the efficacy of closed-loop under more chal-

lenging situations that people with type 1 diabetes may face in their day to day lives. One such scenario is consuming a large meal and alcohol on an evening out, associated with increased risk of postprandial hyperglycaemia and delayed hypoglycaemia, respectively. Subjects consumed a 100g-carbohydrate evening meal accompanied by a moderate amount of white wine (mean 564ml) on two occasions. Closed-loop was applied from 22:00 until lunchtime the next day on one visit, and usual pump therapy continued on the other visit.

In Chapter 4, I describe the first randomised study in pregnant women with type 1 diabetes comparing closed-loop insulin delivery with conventional CSII, during normal daily activities. Maintenance of tight glycaemic control during pregnancy is critical to achieving favourable obstetric outcomes. Daytime control may be especially challenging as a result of the fluctuations in glucose levels that occur with meals and physical activity. Twelve women were evaluated over 24 hours on two visits, including meals, snacks, low intensity self-paced walks and moderate intensity exercise.

As part of the closed-loop study presented in Chapter 4, women were asked to wear an accelerometer and glucose sensor during study visits and at home for up to three days, enabling objective collection of data which was analysed retrospectively. Chapter 5 describes results on activity patterns, physical activity energy expenditure and glucose control in ten pregnant women during free-living, compared with controlled meals and scheduled exercise during a 24 hour period in hospital.

In Chapter 6, I present an assessment of the accuracy of continuous glucose monitoring during moderate intensity exercise in 12 pregnant women with type 1 diabetes, undertaken as part of the closed-loop study discussed in Chapter 4. Glucose sensor values were evaluated against plasma glucose (reference) measured during afternoon and morning sessions of brisk treadmill walking, and compared with sedentary conditions.

Chapter 7 summarises the results of my studies including strengths and limitations, and discusses future plans. I also present the challenges to be overcome prior to introduction of closed-loop into clinical practice.

# Chapter 2

# Feasibility of overnight closed-loop insulin delivery

## 2.1 Background

Maintenance of normal glucose concentrations may significantly reduce diabetes-related complications. However, tight control is associated with an increased risk of hypoglycaemia,[50] such that episodes of and/or the fear of hypoglycaemia limit the ability of patients and their families to achieve target glucose levels.[126] A recent survey of CSII-treated adults in the UK found that 27% had substantial fear of hypoglycaemia, but this was not correlated with higher HbA1c.[127] The experience of hypoglycaemia can have several negative effects, including a feeling of loss of control and heightened anxiety. This may lead to over-compensatory behaviours such as taking less insulin or overeating, resulting in increased blood glucose variability. In the DCCT, intensive therapy lowered mean absolute HbA1c by 2% and mean blood glucose by 5 mmol/l, but also increased the risk of severe hypoglycaemia threefold. Risk factors included low HbA1c, prior history of severe hypoglycaemia, missed meals and change in insulin dose.[119]

Patients with type 1 diabetes suffer two symptomatic episodes of hypoglycaemia per week on average and at least one episode of severe hypoglycaemia, defined as an event requiring assistance of another person to administer rescue treatment, per year.[128; 129] Risk factors for hypoglycaemia include excess or ill-timed therapeutic insulin, decreased exogenous glucose (e.g. missed meals, overnight), increased glucose utilisation (e.g. exercise, pregnancy), decreased endogenous glucose production (e.g. alcohol ingestion), and changes in insulin sensitivity (e.g. weight loss,

exercise).[130]

Hypoglycaemia in healthy individuals is associated with several defence mechanisms including reduced insulin release, and increased glucagon, epinephrine and cortisol secretion. Onset of neuroglycopaenic symptoms including palpitations, tremor, sweating and hunger result in carbohydrate ingestion. In type 1 diabetes, elevated therapeutic insulin levels, an absent rise in glucagon and a higher glycaemic threshold for release of adrenaline contribute to severely compromised counter-regulatory responses to hypoglycaemia. In addition, almost 25% of patients develop hypoglycaemia unawareness, associated with longer disease duration and increased frequency of hypoglycaemic episodes, where there is loss of the autonomic warning symptoms of low glucose.[130] The presence of hypoglycaemia unawareness increases the risk of severe hypoglycaemia six-fold.[131] In the DCCT, 36% of all daytime episodes of severe hypoglycaemia occurred without any warning signs.[119]

Counter-regulatory responses to hypoglycaemia, including epinephrine release, are reduced during sleep.[132] Hypoglycaemia may impair arousal from sleep,[133] although this was not observed in a more recent study.[134] In the DCCT, 55% of severe hypoglycaemia events occurred during sleep, predominantly between midnight and 08:00.[119] Overall, 70% of episodes occurred either during sleep or without recognition of warning symptoms of hypoglycaemia, with no difference between intensive and standard therapy. In the multicentre JDRF CGM trial, hypoglycaemia occurred on 8.5% of 36,467 nights, with 23% of episodes lasting two hours or more and only 3% of patients not experiencing any nocturnal hypoglycaemia.[135] Notably, there was no difference between MDI and CSII-treated patients. Hypoglycaemia risk was correlated with lower HbA1c and higher frequency of hypoglycaemia at baseline.

Nocturnal hypoglycaemia may be associated with cardiac rhythm disturbances, including sinus bradycardia and ectopics.[136] In extreme cases, sudden death may result. This phenomenon, termed 'dead in bed' syndrome, was first described in 1991 and is thought to be responsible for 6% of deaths in patients with type 1 diabetes younger than 40 years of age.[137] Postulated mechanisms include prolongation of the cardiac QTc interval, reduction in extracellular potassium, increase in intracellular calcium, and excess sympathetic activity. The risk of cardiac arrhythmia is increased in the presence of autonomic neuropathy and pre-existing cardiac disease, and may be correlated with male gender, elevated HbA1c, high insulin doses and low body mass index.[138] However, the discordance between prevalence of hypoglycaemia and sudden death suggests other contributory factors such as genetic predisposition.

Severe hypoglycaemia may infrequently result in seizures.[129] The risk of seizure

is increased two to four hours after onset of nocturnal hypoglycaemia.[46] The short and long term consequences of hypoglycaemia on cognitive function are not well understood. Fatigue and an impaired sense of well-being have been observed the morning following overnight hypoglycaemia.[139] Although negative long term effects of hypoglycaemia have been reported,[140] a follow up study to the DCCT found no evidence of decline in cognitive capacity after 18 years in 85% of enrolled patients, despite relatively high rates of severe hypoglycaemia.[141]

## 2.2 Rationale

Improving glucose control whilst asleep, when risk of hypoglycaemia is greatest and the counter-regulatory response to hypoglycaemia is blunted, may be of considerable benefit. The emergence of new technologies including smart insulin pumps and CGM has contributed to improved diabetes care. Despite such advances, existing insulin replacement regimens commonly fail to achieve optimal glycaemic targets.[55] Fine tuning of insulin regimens is only feasible during the daytime whilst awake. CGM provides detailed information in real-time on glucose values and trends, including direction and rate of change.[37] The benefits gained from CGM are dependent on compliance with wearing the device as well as the ability of the user to correctly interpret the glucose values and make appropriate lifestyle and therapy modifications. This is not practical during the night whilst asleep when the majority of severe hypoglycaemia events in adults are reported to occur.[119] Despite the ability to set individual alarms for impending hypoglycaemia, the majority of CGM alarms are not heard by the wearer during sleep.[45]

Combining insulin pumps and glucose sensors may improve diabetes control.[33] However, this still demands considerable patient participation and even the most diligent patients may struggle to achieve optimal glycaemic control. The requirement for multiple testing and adjustment of insulin infusions may be minimised with an artificial pancreas or closed-loop insulin delivery system, which combines real-time continuous glucose sensing with subcutaneous insulin pump delivery, directed by a control algorithm. Use of closed-loop overnight, when glycaemic control is not complicated by meals or physical activity, may be a realistic first step. Such a system has been evaluated in young people with type 1 diabetes, demonstrating improvement in overnight glucose control and reduced nocturnal hypoglycaemia.[104] There are no randomised studies evaluating closed-loop insulin delivery in adults with type 1 diabetes.

## 2.3 Aim

The aim of this study was to assess the feasibility and efficacy of overnight closed-loop insulin delivery compared with conventional continuous subcutaneous insulin infusion (CSII) in adults with type 1 diabetes, in a controlled setting.

## 2.4 Methods

### 2.4.1 Participants

Between February and July 2009, 13 patients were recruited from the adult diabetes outpatient clinic at Addenbrooke's Hospital, Cambridge, UK to take part in the study conducted at the Wellcome Trust clinical research facility, a purpose-built research unit at Addenbrooke's Hospital. The study protocol was approved by the Cambridgeshire Research Ethics Committee, and carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant.

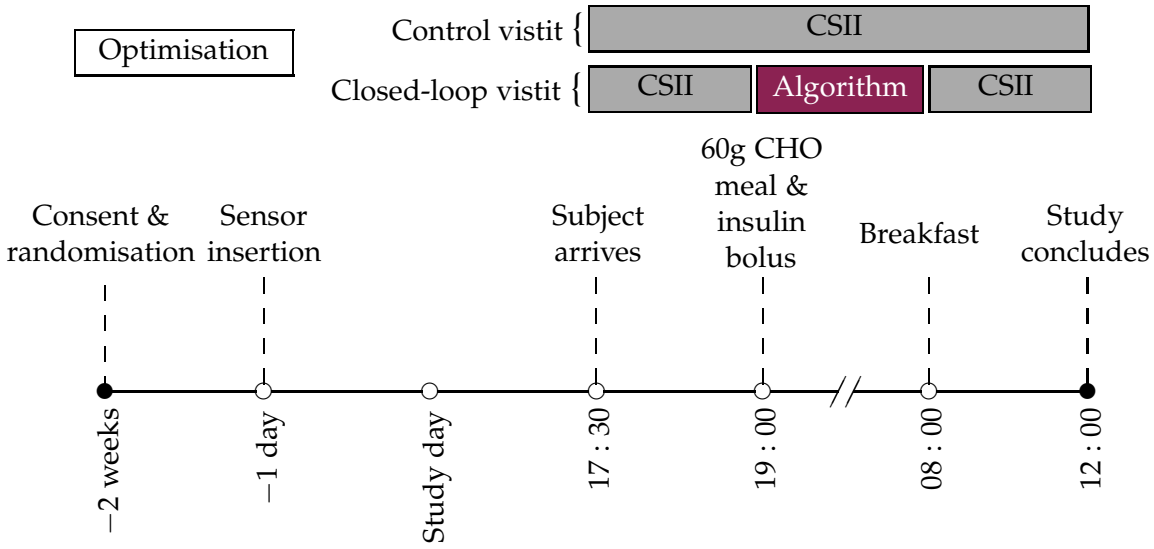
The eligibility criteria for participation included adults (aged 18 to 65 years inclusive) with type 1 diabetes (World Health Organisation definition) for at least six months, and on insulin pump therapy for at least three months prior to the start of the study. Patients were excluded if they had non-autoimmune diabetes, major conditions or concurrent medications likely to interfere with interpretation of the results, clinically significant diabetes-related complications or recurrent severe hypoglycaemia.

### 2.4.2 Study design

The study had a randomised crossover design (Figure 2.1). Once consented, participants were randomised to the order in which two overnight studies were performed, during which glucose levels were controlled either by conventional CSII (control), or by computer-based algorithm (closed-loop). In between study nights, self-adjustment of CSII was permitted, although not encouraged.

Subjects underwent a period of optimisation of glycaemic control at least two weeks prior to the first study night, where they were asked to wear a FreeStyle Navigator CGM (Abbott Diabetes Care, Alameda, CA, USA) for up to five days (Figure 1.1). The device was inserted either in the clinic or at the subject's home, and instructions on use of the device, including alarms and timing of calibrations, were provided to each subject. The CGM data was downloaded and reviewed by the pump clinician

Figure 2.1: Timeline of study procedures




**Notes:** Closed-loop and control (CSII) interventions were carried out in random order, with a one to three week interval between visits.

and pump educator, and participants were subsequently advised if any changes to their insulin pump schedule were required.

One to two days prior to each study night, the sensor was reinserted, in the blinded mode, hence subjects were unable to use CGM to make alterations to their insulin regimen.

On arrival at the clinical research facility, the subject's insulin pump was disconnected and the study pump Deltec Cozmo (Smiths Medical, St Paul, MN, USA) connected to the established subcutaneous insulin infusion site delivering rapid acting insulin analogue Aspart (Novo Nordisk, Bagsvaerd, Denmark). An intravenous cannula was inserted into an antecubital vein for blood sampling of plasma glucose and plasma insulin, at 15 and 30 minute intervals respectively, from 18:30 until study completion at midday the following day. Closed-loop was applied from 19:00 until 08:00. On the control night, subjects continued their usual insulin pump regimen. On both nights, following the meal at 19:00, subjects were able to relax (e.g. read, watch television, work on a computer) in the clinical research facility for the rest of

the evening, and go to bed according to their preference. Subjects were allowed to sleep until breakfast at 08:00. The nursing staff were careful to avoid disturbing the subjects when taking blood samples from the cannula overnight.

#### 2.4.2.1 Meals and insulin bolus

On both study visits subjects consumed a 60g carbohydrate mixed meal (50% carbohydrate, 30% fat, 20% protein) at 19:00. Subjects made their choice prior to study visits from a selection of five meals. The meals offered were similar to what might be consumed at home, and were prepared in advance by dietetic staff in the hospital. The meals were identical on both study nights. The prandial insulin bolus was determined manually by subjects, based on results of fingerprick glucose testing and information on the size of the meal in grams carbohydrate, using their own pump bolus wizard calculator or insulin-carbohydrate ratios. No additional input was provided by study clinicians. At 08:00, subjects consumed a breakfast meal of their own choice with a corresponding insulin bolus also calculated manually. The breakfast was matched on both visits. No snacks or caloric drinks were permitted in between meals until the end of the study visit at midday. Meals and rescue carbohydrate consumed for hypoglycaemia were announced to the algorithm.

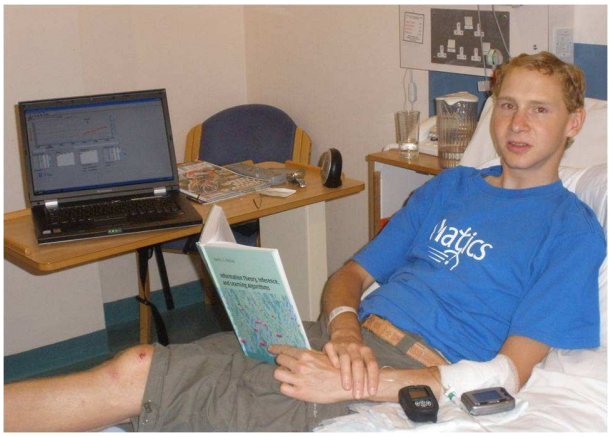
#### 2.4.2.2 Hypoglycaemia

Symptomatic hypoglycaemia or sensor readings below 3.0 mmol/l, confirmed with plasma glucose measurement, were treated with 15g of quick-acting carbohydrate in the form of Lucozade Energy drink (GlaxoSmithKline, UK) or orange juice. Plasma glucose was repeated 15 minutes after rescue treatment and further 15g given if biochemical or symptomatic hypoglycaemia persisted. Intravenous dextrose was available to treat persisting hypoglycaemia not responding to oral carbohydrates. If there were more than two such episodes or if there was a single plasma glucose value below 2.0 mmol/l, the study visit was discontinued.

#### 2.4.2.3 Randomisation and blinding

Block randomisation was used, the sequence produced by a computer-generated random code, to allocate subjects to the order in which they completed their algorithm and control nights. The second visit was completed within one to three weeks in a crossover design. Subjects were blinded to CGM and plasma glucose values on both visits. Investigators were blinded to plasma glucose values only.

Figure 2.2: Participant during closed-loop study



**Notes:** The Deltec Cozmo insulin pump and receiver component of the FreeStyle Navigator glucose sensor are shown in the foreground, with the laptop computer running the control algorithm in the background.

#### 2.4.2.4 Closed-loop visit

The closed-loop system, shown in Figure 2.2, was employed for 13 hours in total, from 19:00 until 08:00 the following day. Every 15 minutes, the sensor glucose value was read and entered by the research nurse or clinician into a laptop computer at the subject's bedside, containing the algorithm. The insulin infusion rate to be delivered over the next 15 minutes was computed by the algorithm, and subsequently adjusted manually on the study pump.

- **Continuous glucose sensor.** The FreeStyle Navigator CGM (Abbott Diabetes Care, Alameda, CA, USA), calibrated with capillary glucose measurements on the inbuilt meter as per manufacturers' instructions, was used. The sensor was inserted at least 24 hours prior to each study visit, as the device had a run-in period of 10 hours prior to displaying glucose values.

- **Model Predictive Control (MPC) algorithm.** An adaptive model predictive control (MPC) algorithm designed at the University of Cambridge was used. Versions 0.02.04.0 to 0.02.13.0 were used during the study. The MPC algorithm employs a compartment model of glucose kinetics representing the effect of rapid acting insulin and the amount of carbohydrate consumed on sensor glucose excursions.[81] Information regarding subject's body weight, total daily in-

sulin dose, and basal insulin infusion rates are entered into the computer prior to commencement of the algorithm. In real-time, sensor glucose measurements are used to update two model parameters: an endogenous glucose flux correcting for errors in model-based predictions, and carbohydrate bioavailability. A combined model forecasts plasma glucose excursions over a 2.5 hour prediction horizon. Insulin infusion is calculated to achieve the target glucose, which is set at 5.8 mmol/l but may increase up to 7.3 mmol/l if model-based predictions are considered less accurate. Intrinsic safety rules reduce insulin infusion to prevent overdosing if required.

- **Study pump.** The Deltec Cozmo pump (Smiths Medical, St Paul, MN, USA) was used on all study visits. Subjects were asked to replace their usual insulin infusion set, normally changed every three days, approximately 24 hours prior to each study visit. The rapid acting insulin analogue aspart (Novo Nordisk, Bagsvaerd, Denmark) was used for all study visits to ensure comparability. Subjects usually on insulin lispro (Eli Lilly, Indianapolis, USA) were asked to switch to aspart at least 24 hours prior to each study visit.

#### 2.4.2.5 CSII visit

On the CSII visit, subjects continued their insulin pump regimen, similar to a night at home. On arrival for the study visit, usual pre-programmed basal infusion rates were entered into the study pump which was used for insulin delivery from 19:00 until 12:00 the following day.

### 2.4.3 Measurements

Whole blood samples for glucose and insulin were immediately centrifuged and stored frozen for later analysis. Plasma glucose was measured on a Yellow Springs International YSI 2300 STAT Plus analyser (YSI Ltd, Farnborough, UK). The intra-assay coefficient of variation (CV), was 1.5% at 4.1 mmol/l. Plasma glucose values were not used to change insulin doses for delivery during closed-loop, with infusion rates calculated based on sensor glucose readings alone. Plasma insulin was measured using an immunochemiluminometric assay (Invitron Ltd, Monmouth, UK) which had a mean intra-assay CV of 4.7% and inter-assay CV of $7.2 - 8.1\%$ between $3.3 - 133$ mU/l.

### 2.4.4 Statistical analysis

#### 2.4.4.1 Power calculation

The power calculation was based on results of the study of closed-loop in children with type 1 diabetes.[104] Assuming a similar standard deviation of 40% and a two sided significance level of 0.05, a sample size of 12 provided 80% power to detect an absolute increase in proportion of time spent in target glucose ($3.9 - 8.0$ mmol/l) of 37% (from 26% during CSII to 63% during closed-loop).

#### 2.4.4.2 Efficacy endpoints

The primary outcome measure was proportion of time spent with plasma glucose in target range defined as $3.9 - 8.0$ mmol/l, between 19:00 and 08:00. Secondary outcomes were time spent below ($< 3.9$ mmol/l) and above ($> 8.0$ mmol/l) target, mean glucose, and glycaemic variability as measured by standard deviation of overnight glucose. In addition, the low blood glucose index and high blood glucose index assessing the duration and extent of hypo- and hyperglycaemia, respectively, were calculated.[97] Mean basal insulin infusion rate and plasma insulin concentration were measured to enable comparison of insulin delivery on both study visits, and provide information on insulin kinetics. Secondary outcomes were calculated using plasma and sensor (CGM) glucose, for the following time periods:

- **Overall period (19:00-08:00).** On closed-loop visits, the 'overall period' was defined as the interval from commencement of the algorithm at 19:00 with the evening meal until discontinuation at 08:00 the following morning. On CSII visits, this was defined as the corresponding period in time when subjects continued their usual CSII regimen.

- **Overnight period (00:00-08:00).** On closed-loop visits, the 'overnight period' was defined as the period from midnight until discontinuation of the algorithm at 08:00. This period was chosen as it was several hours after the prandial insulin bolus, hence allowing evaluation of performance of closed-loop with minimal influence of bolus insulin. On CSII visits, this was the corresponding period in time when subjects continued their usual CSII regimen.

- **Morning period (08:00-12:00).** On closed-loop visits, the 'morning period' was defined from 08:00 when subjects discontinued the algorithm and resumed their

usual CSII regimen, until study end at midday. On CSII visits, subjects continued their usual CSII regimen from 08:00 until study end. This period was chosen as it enabled evaluation of any persisting effect of the algorithm on glycaemic control after its discontinuation.

Plasma glucose values were interpolated to one minute between each 15 minute sample. Missing plasma glucose values were also interpolated when measurements were available before and after the missing value. Analyses were carried out using SPSS, Version 15 (SPSS Inc, Chicago, IL, USA). Each set of outcome data was assessed for normality using Q-Q plots. For normally distributed results, values are given as mean and standard deviation and evaluated using two-sided paired *t*-tests. For non-normal distributions, median and interquartile range were calculated with significance levels analysed using the Wilcoxon non-parametric *t*-test. Statistical significance was indicated by $p < 0.05$. Individual paired sensor and reference glucose values were plotted using the Clarke error grid analysis.[10]

## 2.5 Results

Of the 32 patients that were screened, 13 subjects were enrolled. One subject dropped out after their first study visit, hence was replaced, and their results not included in further analyses.

The subject demographics are summarised in Table 2.1. The mean HbA1c, measured within three months of study commencement, ranged from 7.1% to 8.7%. The average duration of type 1 diabetes ranged from 3.9 to 35.4 years, and mean time on CSII therapy from 0.4 to 13.3 years. The average time between study visits was $14 \pm 7$ days.

### 2.5.1 Primary outcome

The primary outcome measure of time spent with plasma glucose values in target ($3.9 - 8.0$ mmol/l) between 19:00 and 08:00 was 81% during closed-loop compared with 57% during conventional CSII; $p = 0.012$ (Table 2.2).

Figure 2.3 displays the proportion of glucose values within, below and above target ($3.9 - 8.0$ mmol/l) for the overall study period during both interventions. As indicated by the numbers at the top, there was a greater probability of glucose being within target during closed-loop (72% versus 52%) and lower probability of being in hypoglycaemic or hyperglycaemic range (Figure 2.3).

Table 2.1: Demographics of 12 participants

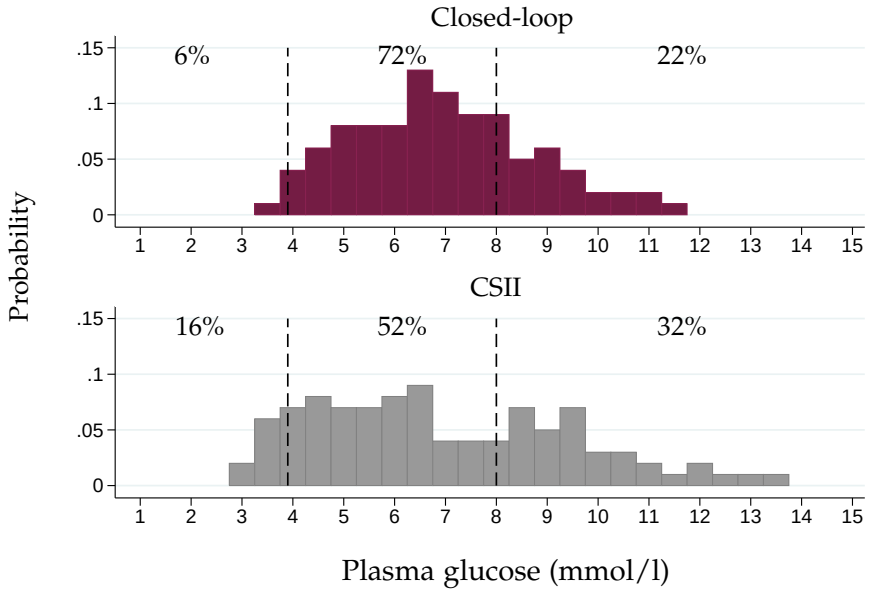
| Characteristic | Number of subjects | Mean | Standard deviation |
|---|---|---|---|
| Sex (male/female) | 5/7 | | |
| Age (years) | | 37.7 | 8.5 |
| Body mass index (kg/m$^2$) | | 24.6 | 2.6 |
| Weight (kg) | | 72.8 | 9.3 |
| HbA1c (%) | | 7.8 | 0.5 |
| Duration of diabetes (years) | | 21.5 | 10.1 |
| Duration on pump (years) | | 2.9 | 3.5 |
| Insulin used (aspart/lispro) | 4/8 | | |
| Total daily insulin (U) | | 38.2 | 10.4 |
| Total daily basal (U) | | 18.3 | 6.6 |
| Total daily bolus (U) | | 19.9 | 6.6 |
| Total daily insulin/kg (U) | | 0.5 | 0.1 |

Table 2.2: Time spent with plasma glucose in target during closed-loop and CSII, for overall, overnight and morning periods

| | | 3.9 $<$ Plasma glucose $\leq$ 8.0 mmol/l (%) | |
|---|---|---|---|
| Period | | Median | Interquartile range |
| Overall (19:00-08:00) | CL | 81 | (50,95) |
| | CSII | 57 | (36,81) |
| | P-value | 0.012* | |
| Overnight (00:00-08:00) | CL | 89 | (66,100) |
| | CSII | 48 | (33,92) |
| | P-value | 0.007* | |
| Morning (08:00-12:00) | CL | 62 | (20,95) |
| | CSII | 22 | (2,32) |
| | P-value | 0.041* | |

**Notes:** * Denotes statistical significance at the 5% level.

Figure 2.3: Distribution of plasma glucose during closed-loop and CSII




**Notes:** Percent values denote proportion of plasma glucose values below, within and above target (3.9 – 8.0 mmol/l).

### 2.5.2 Secondary outcomes

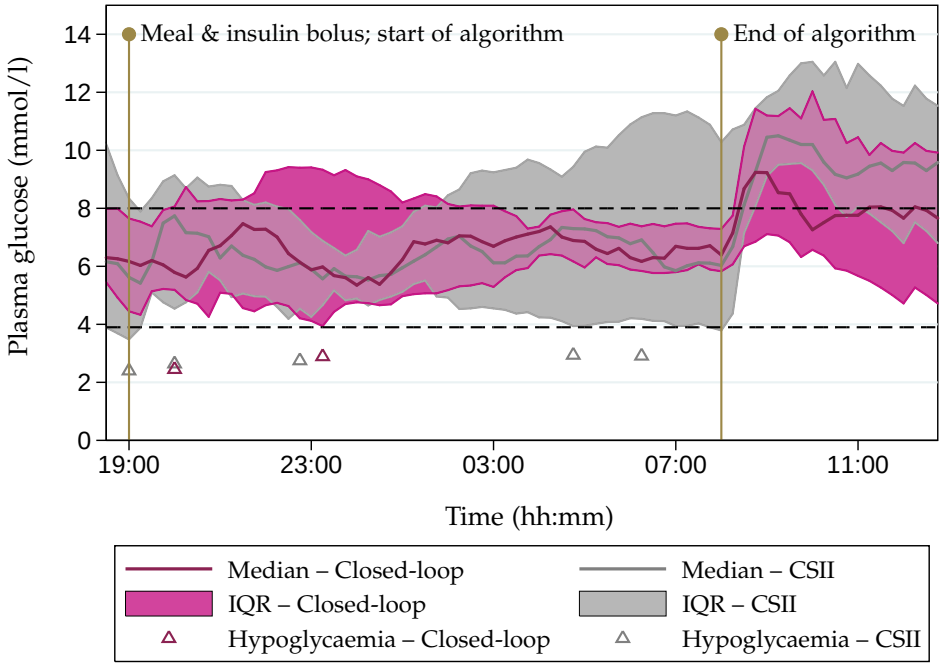
#### 2.5.2.1 Average glucose and variability

Secondary analysis of the period from midnight to 08:00 demonstrated greater efficacy of closed-loop, with 89% of time spent in target plasma glucose range compared with 48% during CSII (Table 2.2).

There was no difference in the mean overnight plasma glucose; 6.7 mmol/l versus 6.8 mmol/l; $p = 0.941$ (Table 2.3). The median plasma glucose trends during closed-loop and CSII visits were similar and remained within target range between 19:00 and 08:00 (Figure 2.4).

The overall standard deviation of plasma glucose, indicating glycaemic variability, was significantly lower during closed-loop; 1.2 mmol/l versus 1.7 mmol/l; $p = 0.003$ (Table 2.3). This is illustrated in Figure 2.4 by the interquartile range of glucose which was similar between closed-loop and CSII in the first few hours following the evening meal, but was considerably narrower during overnight closed-loop from

Figure 2.4: Plasma glucose profiles during closed-loop and CSII




approximately 02:00 until 08:00.

Secondary outcomes calculated using sensor glucose are summarised in Table 2.4. Using sensor glucose as an outcome measure indicated an even higher time in target during closed-loop (93%) compared with CSII (63%).

Individual plasma and sensor glucose profiles for each subject are shown in Appendix A.

#### 2.5.2.2 Hypoglycaemia

Closed-loop insulin delivery halved the low blood glucose index; 0.8 versus 1.7, $p = 0.019$ (Table 2.3). Additionally, there was a non-significant reduction in time spent below 3.9 mmol/l during closed-loop; 2% versus 4%, $p = 0.066$. No time was spent below 3.0 mmol/l during either intervention (Figure 2.3). Overall, there were five plasma glucose values below 3.0 mmol/l during closed-loop and 15 on CSII (Table 2.5). After midnight, there were no plasma glucose measurements below 3.5 mmol/l during closed-loop compared with 37 (9.4%) during CSII. The lowest recorded plasma

Table 2.3: Plasma glucose outcomes during closed-loop and CSII, for overall, overnight and morning periods

| | Overall (19:00-08:00) | | | Overnight (00:00-08:00) | | | Morning (08:00-12:00) | | |
|---|---|---|---|---|---|---|---|---|---|
| | CL | CSII | P-value | CL | CSII | P-value | CL | CSII | P-value |
| Plasma glucose at start of CL (mmol/l) | $6.6 \pm 1.9$ | $6.9 \pm 3.4$ | 0.776 | — | — | — | — | — | — |
| Mean plasma glucose (mmol/l) | $6.7 \pm 1.4$ | $6.6 \pm 1.3$ | 0.889 | $6.7 \pm 1.3$ | $6.8 \pm 2.2$ | 0.941 | $8.2 \pm 2.2$ | $9.3 \pm 2.0$ | 0.244 |
| Standard deviation of plasma glucose (mmol/l) | 1.2 (1.0,1.4) | 1.7 (1.4,2.5) | 0.003* | 0.9 (0.6,1.2) | 1.0 (0.5,1.9) | 0.480 | 1.3 (0.6,2.1) | 1.5 (1.1,2.3) | 0.050* |
| $3.9 <$ Plasma glucose $\leq 8.0$ mmol/l (%) | 81 (50,95) | 57 (36,81) | 0.012* | 89 (66,100) | 48 (33,92) | 0.007* | 62 (20,95) | 22 (1.7,32) | 0.041* |
| Plasma glucose $< 3.0$ mmol/l (%) | 0 (0,0) | 0 (0,7) | 0.225 | 0 (0,0) | 0 (0,0) | 0.285 | 0 (0,0) | 0 (0,0) | 0.317 |
| Plasma glucose $\leq 3.9$ mmol/l (%) | 2 (0,8) | 4 (0,27) | 0.066 | 0 (0,2) | 0 (0,25) | 0.225 | 0 (0,0) | 0 (0,12) | 0.600 |
| Plasma glucose $> 8.0$ mmol/l (%) | 10 (1,48) | 24 (14,46) | 0.117 | 2 (0,30) | 22 (0,67) | 0.018* | 34 (0,80) | 75 (53,98) | 0.110 |
| Low blood glucose index | 0.8 (0.0,1.9) | 1.7 (0.4,4.9) | 0.019* | 0.1 (0.0,1.2) | 0.5 (0.1,5.4) | 0.092 | 0.0 (0.0,0.5) | 0.0 (0.0,1.6) | 0.674 |
| High blood glucose index | 1.0 (0.3,3.0) | 1.4 (0.9,4.4) | 0.306 | 0.8 (0.2,1.9) | 1.1 (0,5.1) | 0.091 | 1.6 (0.5,7.7) | 7.4 (3.4,12.0) | 0.050* |

**Notes**: Data are mean $\pm$ standard deviation or median (interquartile range). * Denotes statistical significance at the 5% level.

Table 2.4: Sensor glucose outcomes during closed-loop and CSII, for overall, overnight and morning periods

| | Overall (19:00-08:00) | | | Overnight (00:00-08:00) | | | Morning (08:00-12:00) | | |
|---|---|---|---|---|---|---|---|---|---|
| | CL | CSII | P-value | CL | CSII | P-value | CL | CSII | P-value |
| Sensor glucose at start of CL (mmol/l) | $6.6 \pm 1.9$ | $6.6 \pm 2.4$ | 0.859 | — | — | — | — | — | — |
| Mean sensor glucose (mmol/l) | $6.6 \pm 0.7$ | $6.7 \pm 1.3$ | 0.814 | $6.5 \pm 0.7$ | $6.4 \pm 2.2$ | 0.695 | $8.1 \pm 1.7$ | $9.0 \pm 2.0$ | 0.272 |
| Standard deviation of sensor glucose (mmol/l) | 1.0 (0.7,1.3) | 1.4 (1.0,2.5) | 0.071 | 0.8 (0.5,0.9) | 0.7 (0.7,1.6) | 0.480 | 1.1 (0.6,1.8) | 1.3 (1.1,1.7) | 0.239 |
| $3.9 <$ Sensor glucose $\leq 8.0$ mmol/l (%) | 93 (82,100) | 63 (46,75) | 0.004* | 99 (82,100) | 49 (32,78) | 0.005* | 68 (16,95) | 21 (3,67) | 0.158 |
| Sensor glucose $< 3.0$ mmol/l (%) | 0 (0,0) | 0 (0,0) | 0.285 | 0 (0,0) | 0 (0,0) | 0.180 | 0 (0,0) | 0 (0,0) | 0.317 |
| Sensor glucose $\leq 3.9$ mmol/l (%) | 0 (0,4) | 2 (0,27) | 0.123 | 0 (0,0) | 1 (0,42) | 0.075 | 0 (0,0) | 0 (0,2) | 0.109 |
| Sensor glucose $> 8.0$ mmol/l (%) | 4 (0,16) | 17 (11,38) | 0.021* | 0 (0,18) | 13 (0,62) | 0.028* | 32 (5,84) | 77 (31,87) | 0.272 |
| Low blood glucose index | 0.5 (0.2,0.9) | 1.2 (0.4,4.4) | 0.016* | 0.4 (0.0,0.6) | 1.5 (0.0,6.6) | 0.021* | 0.0 (0.0,0.1) | 0.1 (0.0,0.9) | 0.192 |
| High blood glucose index | 0.5 (0.2,0.9) | 1.2 (0.5,2.7) | 0.018* | 0.3 (0.2,0.8) | 0.9 (0.0,3.9) | 0.135 | 1.7 (0.5,7.4) | 6.9 (1.8,11.5) | 0.224 |

**Notes**: Data are mean $\pm$ standard deviation or median (interquartile range). * Denotes statistical significance at the 5% level.

Table 2.5: Plasma glucose values in hypoglycaemic range during closed-loop and CSII for overall (19:00-08:00) and overnight (00:00-08:00) periods

| | Overall $N = 636$ | | | | Overnight $N = 396$ | | | |
|---|---|---|---|---|---|---|---|---|
| Plasma glucose | CL | | CSII | | CL | | CSII | |
| (mmol/l) | $n$ | % | $n$ | % | $n$ | % | $n$ | % |
| $< 2.00$ | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| $2.00 - 2.49$ | 2 | 0.3 | 3 | 0.5 | 0 | 0.0 | 0 | 0.0 |
| $2.50 - 2.99$ | 3 | 0.5 | 12 | 1.9 | 0 | 0.0 | 5 | 1.3 |
| $3.00 - 3.49$ | 4 | 0.6 | 41 | 6.4 | 0 | 0.0 | 32 | 8.1 |
| $3.50 - 3.89$ | 23 | 3.6 | 29 | 4.6 | 7 | 1.8 | 18 | 4.5 |
| Total $< 3.9$ | 32 | 5.0 | 85 | 13.4 | 7 | 1.8 | 55 | 13.9 |

**Notes:** $N$ denotes total number of plasma glucose values, and $n$ denotes number of plasma glucose values $< 3.9$ mmol/l, within the specified period.

glucose was 2.3 mmol/l and there were no values below 2.0 mmol/l during both closed-loop and CSII visits.

During the total 24 study visits, there were seven hypoglycaemic events, defined as plasma glucose $< 3.0$ mmol/l: two during closed-loop and five during CSII (Table 2.6 and Figure 2.4). Four episodes resolved spontaneously within an hour and three were treated with $15 - 36$g of quick-acting carbohydrate. There was no requirement for intravenous dextrose infusion on any episode. Three events were asymptomatic, two of which occurred in the middle of the night. Both episodes during closed-loop occurred before midnight, and were likely related to the insulin bolus administered with the evening meal.

Subject 1 had a hypoglycaemic episode on both their closed-loopand CSII visits. These occurred at a similar time on both visits, within an hour of consuming the evening meal, hence the hypoglycaemia was attributed to miscalculation of the prandial insulin bolus. Subject 13 experienced two hypoglycaemic events on their CSII visit, the second occurring six hours after the first treated episode. There was one deviation from study protocol where a subject had hypoglycaemic symptoms and self-treated with orange juice, despite advice that plasma glucose measured at the time was 3.6 mmol/l and hence above the threshold for treatment. This was not classified as an episode of hypoglycaemia.

Table 2.6: Detail of all hypoglycaemia episodes

| Study visit | Subject | Plasma glucose (mmol/l) | Time | Duration (min) | Symptoms (Yes/No) | Treated (Yes/No) | CHO (g) |
|---|---|---|---|---|---|---|---|
| CL | 1 | 2.45 | 20:00 | 45 | Y | Y | 36 |
| CL | 8 | 2.89 | 23:15 | 30 | Y | N | |
| CSII | 1 | 2.64 | 20:00 | 60 | Y | Y | 18 |
| CSII | 3 | 2.91 | 06:15 | 15 | N | N | |
| CSII | 4 | 2.40 | 19:00 | 60 | N | N | |
| CSII | 13 | 2.75 | 22:45 | 30 | Y | Y | 15 |
| CSII | 13 | 2.94 | 04:45 | 45 | N | N | |

**Notes:** CHO denotes rescue carbohydrates consumed.

#### 2.5.2.3 Hyperglycaemia

The time spent with plasma glucose above 8.0 mmol/l overall was more than halved during closed-loop; 10% versus 24%, $p = 0.117$ (Table 2.3). There was a greater proportion of values in the higher glucose range ($12 - 14$ mmol/l) during CSII compared with closed-loop (Figure 2.3). After midnight, the benefit of closed-loop in reducing hyperglycaemia was even greater, with less than 2% of time spent above 8.0 mmol/l compared with 22% during CSII; $p = 0.018$. There were no plasma glucose values above 16.6 mmol/l overall. Using sensor glucose outcomes, the improvement in time spent above target glucose during closed-loop was significant (4% versus 17%; $p = 0.021$), in addition to a reduction in the high blood glucose index from 1.2 to 0.5; $p = 0.018$ (Table 2.4).

#### 2.5.2.4 Insulin

There was no difference in the hourly rate (0.7 U/h versus 0.8 U/h; $p = 0.657$) or total amount of insulin infusion (9.6U versus 10.3U; $p = 0.646$) between closed-loop and CSII visits overall (Table 2.7). However, there was much greater variability in infusion rates during closed-loop compared with CSII, reflecting the pattern of glucose-responsive insulin delivery employed by the model predictive control algorithm. Median insulin infused is illustrated in Figure 2.5. Individual basal insulin profiles for each subject are provided in Appendix A. The hourly insulin infusion rates ranged from $0 - 2.6$ U/h during closed-loop and $0.3 - 1.4$ U/h during CSII. The wider range of infusion rates delivered during closed-loop persisted after adjust-

Table 2.7: Summary of plasma insulin and insulin infused during closed-loop and CSII, for overall, latter, morning and postprandial periods

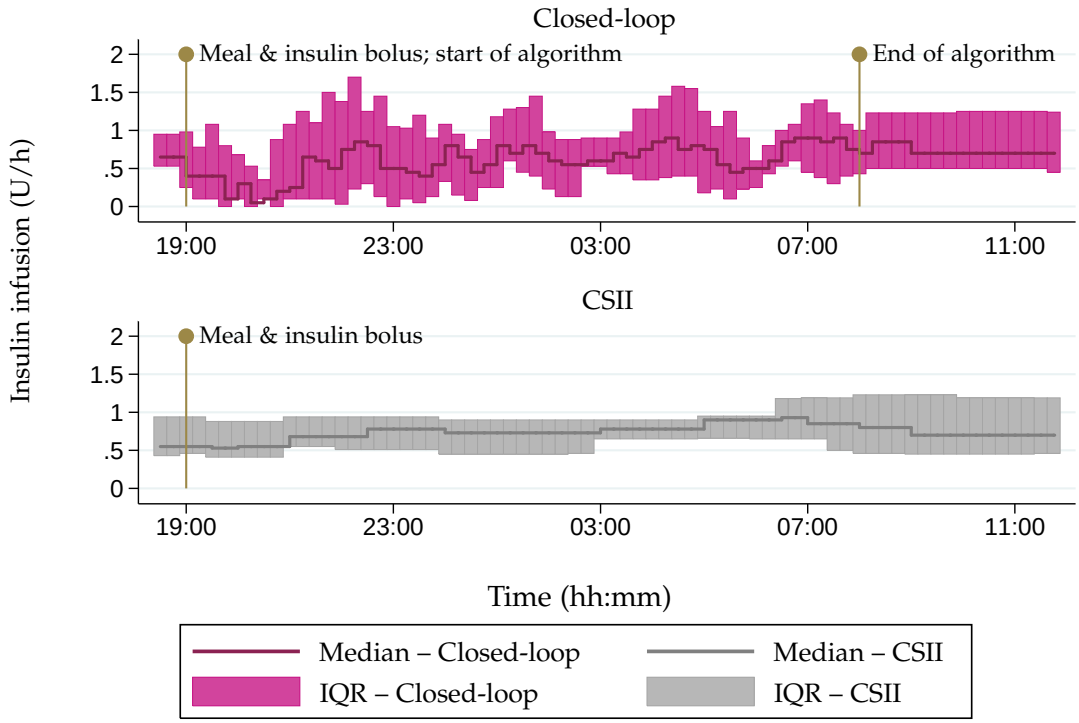
| | | Plasma insulin concentration (pmol/l) | | Insulin infusion (U/h) | | Total insulin administered (U) | |
|---|---|---|---|---|---|---|---|
| Period | | Median | IQR | Median | IQR | Median | IQR |
| Overall (19:00-08:00) | CL | 76 | (51,105) | 0.7 | (0.5,0.9) | 9.6 | (6.3,11.0) |
| | CSII | 96 | (64,132) | 0.8 | (0.6,0.9) | 10.3 | (7.6,11.9) |
| | P-value | 0.060 | | 0.657 | | 0.646 | |
| Overnight (00:00-08:00) | CL | 51 | (31,84) | 0.8 | (0.6,1.0) | 6.3 | (4.5,7.7) |
| | CSII | 70 | (48,84) | 0.8 | (0.6,0.9) | 6.7 | (5.1,7.4) |
| | P-value | 0.480 | | 0.875 | | 0.875 | |
| Morning (08:00-12:00) | CL | 132 | (83,159) | 0.7 | (0.5,1.2) | 2.8 | (1.8,4.8) |
| | CSII | 125 | (76,165) | 0.7 | (0.5,1.2) | 2.8 | (1.9,4.9) |
| | P-value | 0.695 | | 0.916 | | 0.752 | |
| Postprandial (19:00-21:00) | CL | 154 | (111,241) | 0.4 | (0.2,0.7) | 0.8 | (0.5,1.4) |
| | CSII | 174 | (107,223) | 0.6 | (0.5,0.9) | 1.2 | (0.9,1.8) |
| | P-value | 0.638 | | 0.028* | | 0.028* | |

**Notes:** *Denotes statistical significance at the 5% level.

ment for body weight (Figure 2.6).

The measured plasma insulin concentration was comparable on both visits (76 pmol/l closed-loop versus 96 pmol/l CSII; $p = 0.060$), providing further evidence of the similar amount of insulin infused on both study visits (Table 2.7). The plasma insulin peaks in Figure 2.7 correspond to the prandial insulin boluses taken for the evening meal and breakfast. Variability of plasma insulin concentrations is illustrated in Figure 2.7 by the interquartile range. This was greatest in the period following the evening meal, particularly during CSII, and was likely related to the prandial insulin bolus administered. Variability was much lower overnight, on both closed-loop and CSII visits.

Figure 2.5: Insulin infusion rates during closed-loop and CSII

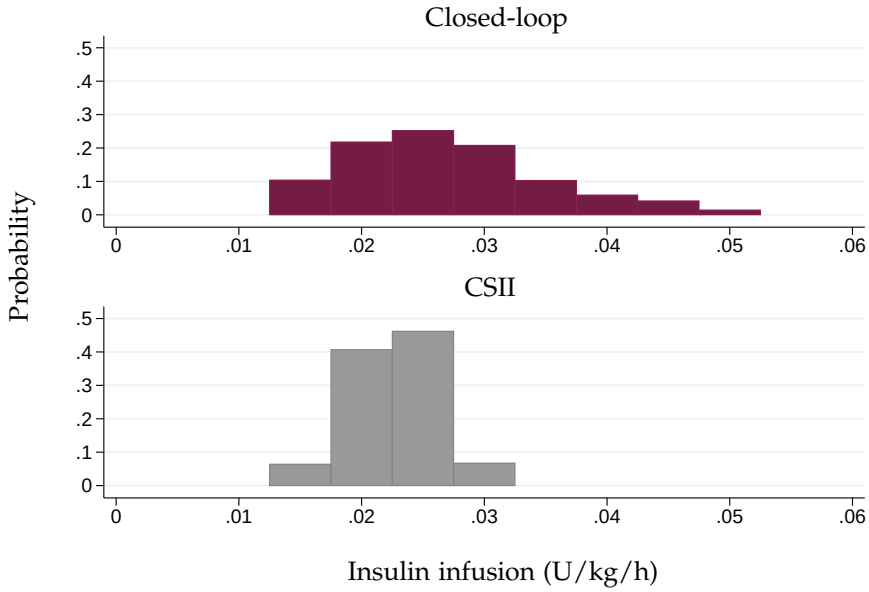



#### 2.5.2.5 Postprandial control

The average quantity of carbohydrates consumed for dinner and breakfast on both study visits are summarised in Table 2.8. One subject was unable to finish their evening meal on one of their visits, consuming only 45g carbohydrate. The carbohydrate content of breakfast, which was self-selected, ranged from 27g to 74g amongst subjects. The breakfast consumed on the first visit was matched on the second visit.

Eight subjects had a simple bolus within five minutes of commencing their evening meal on both study visits (Table 2.9). Two subjects delayed administration of the insulin bolus until after the meal on the CSII visit as their fingerprick glucose was low. Two subjects chose a complex insulin bolus for both study visits: subject 11 used a dual wave, and subject 13 used a square wave bolus (Table 2.9). The mode of insulin delivery was consistent with their standard practice at home, and the inter-

Figure 2.6: Distribution of insulin infusion rates during closed-loop and CSII



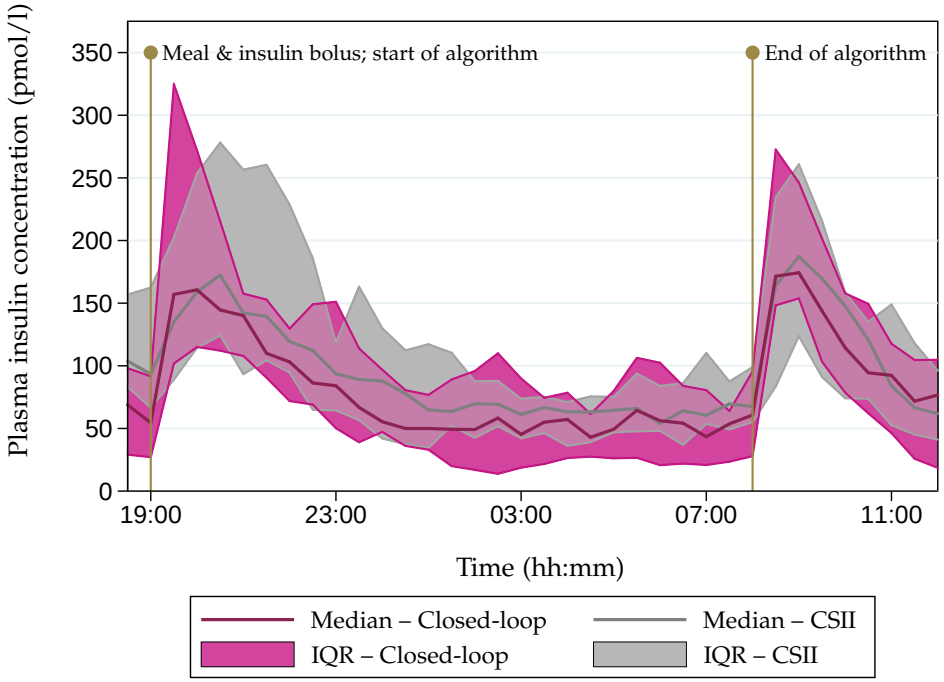

individual variation reflects the wide range of approaches that patients might use to control postprandial glucose levels.

The mean peak plasma glucose measured after consumption of the evening meal was 9.0 mmol/l during closed-loop and 10.2 mmol/l during CSII; $p = 0.076$ (Table 2.8). The average time to maximum glucose was over five hours for both visits. Of note, basal insulin infusion in the postprandial period between 19:00 and 21:00 was significantly lower during closed-loop; 0.4 U/h versus 0.6 U/h, $p = 0.028$ (Table 2.7 and Figure 2.5).

Notably, the peak in plasma insulin concentration following the evening meal occurred earlier during closed-loop compared with CSII, corresponding to the prandial insulin bolus administered (Figure 2.7). The average bolus was slightly higher on closed-loop visits; 5.6U versus 5.2U on CSII, $p = 0.177$ (Table 2.8). The later peak during CSII may be attributed to delayed time of administration of the prandial bolus on two subjects' CSII visits, according to their usual practice for low fingerprick glucose (Table 2.9).

Following breakfast at 08:00, there was a sharp rise in plasma glucose, reaching a higher peak during CSII (11.7 mmol/l versus 10.4 mmol/l; $p = 0.233$). Time

Figure 2.7: Plasma insulin concentration profiles during closed-loop and CSII




to peak was just under 90 minutes during both interventions, which is much faster than observed with the evening meal. Glucose returned to target range below 8.0 mmol/l within 90 minutes after eating during closed-loop visits, but remained elevated around 10.0 mmol/l until study end during CSII visits (Figure 2.4). Notably, basal insulin infusion rates were identical between 08:00 and 12:00 on both visits, as the algorithm was discontinued and subjects resumed their usual CSII at 08:00 on closed-loop visits.

#### 2.5.2.6 Period after closed-loop

The benefits of closed-loop persisted after being discontinued and standard CSII resumed at 08:00, with time in target plasma glucose 62% on closed-loop visits compared with only 22% on CSII; $p = 0.041$ (Table 2.2). Glycaemic variability (standard deviation 1.3 mmol/l versus 1.5 mmol/l; $p = 0.050$) was also lower with closed-loop. The time spent in hyperglycaemia was halved (34% versus 75%; $p = 0.110$), with a significant reduction in the high blood glucose index (1.6 versus 7.4; $p = 0.050$).

Table 2.8: Summary of insulin bolus and peak postprandial glucose for evening meal and breakfast

| | Closed-loop | CSII | P-value |
|---|---|---|---|
| *Evening meal* | | | |
| Carbohydrates (g) | $60 \pm 8$ | $62 \pm 6$ | 0.339 |
| Bolus (U) | $5.6 \pm 1.2$ | $5.2 \pm 1.3$ | 0.177 |
| Peak plasma glucose (mmol/l) | $9.0 \pm 1.8$ | $10.2 \pm 1.8$ | 0.076 |
| Time from start of meal (mins) | $315 \pm 264$ | $338 \pm 295$ | 0.823 |
| *Breakfast* | | | |
| Carbohydrates (g) | $47 \pm 16$ | $47 \pm 16$ | 1.000 |
| Bolus (U) | $4.3 \pm 1.7$ | $4.2 \pm 2.0$ | 0.843 |
| Peak plasma glucose (mmol/l) | $10.4 \pm 2.8$ | $11.7 \pm 2.4$ | 0.233 |
| Time from start of meal (mins) | $85 \pm 63$ | $88 \pm 53$ | 0.915 |

**Notes:** Data are mean $\pm$ standard deviation.

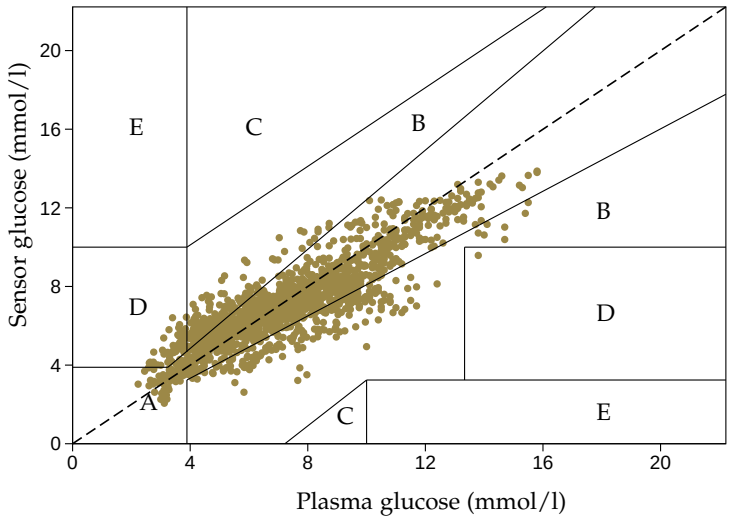
Table 2.9: Insulin bolus administered with evening meal for each subject

| | Closed-loop | | CSII | |
|---|---|---|---|---|
| Subject number[a] | Insulin (U) | Time of bolus (hh:mm) | Insulin (U) | Time of bolus (hh:mm) |
| 1 | 6.6 | 19:00 | 6.6 | 19:00 |
| 2 | 6.0 | 18:59 | 6.0 | 19:04 |
| 3 | 4.6 | 18:59 | 4.6 | 19:03 |
| 4 | 7.5 | 19:00 | 5.0 | 19:02 |
| 5 | 7.5 | 19:00 | 7.5 | 19:31 |
| 6 | 4.8 | 19:00 | 4.8 | 19:00 |
| 7 | 5.0 | 19:01 | 4.0 | 19:00 |
| 8 | 6.0 | 19:00 | 6.0 | 18:59 |
| 10 | 6.0 | 19:00 | 5.0 | 19:01 |
| 11 | 4.5[b] | 19:00 | 5.4[c] | 19:08 |
| 12 | 4.0 | 19:03 | 3.5 | 19:23 |
| 13 | 4.5[d] | 19:03 | 6.0[d] | 19:01 |

**Notes:** [a] Subject 9 withdrew from the study; [b] 2.15U at 19:00 and 2.35U over three hours (dual wave); [c] 3.05U at 19:08 and 2.35U over three hours (dual wave); [d] Delivered over two hours (square wave).

These benefits during closed-loop visits were seen despite identical amount of insulin infused (2.8U; $p = 0.752$), substantiated by similar measured plasma insulin concentrations; 132 pmol/l versus 125 pmol/l, $p = 0.695$ (Table 2.7).

Figure 2.8: Clarke error grid analysis showing accuracy of FreeStyle Navigator CGM




**Notes:** Values in zone A or B are clinically acceptable. Values in zone C, D or E are clinically unsafe.

### 2.5.3 Sensor accuracy

The accuracy of the FreeStyle Navigator CGM (Abbott Diabetes Care, Alameda, CA, USA), evaluated by the median relative absolute difference between paired sensor and reference (plasma) glucose measurements, was 8.0% (4.5%, 19.3%) This is comparable with reported median RAD of 11.8% for the same device.[16] The Clarke error grid analysis displays the paired sensor and reference glucose values (Figure 2.8). The majority of values were in the clinically acceptable zones A and B. Of the values in the clinically unsafe zones, all were in zone D predominantly during hypoglycaemia.

## 2.6 Discussion

This is the first randomised closed-loop study in adults with type 1 diabetes, demonstrating the feasibility and efficacy of overnight closed-loop insulin delivery following a medium-sized evening meal in a controlled setting. Compared with conventional CSII, closed-loop increased the time spent with glucose values in target range

(3.9 − 8.0 mmol/l) by 24%. Glucose variability, which is associated with an increased risk of complications of diabetes was also reduced.[48]

This study confirmed the safety of overnight closed-loop as indicated by the reduced low blood glucose index and a trend towards lesser time spent below 3.9 mmol/l. There were two episodes of hypoglycaemia during closed-loop, compared with five during CSII. Both occurred before midnight and were likely related to the prandial insulin bolus administered with the evening meal. There were no plasma glucose values below 3.5 mmol/l after midnight during closed-loop. One of the features of the model predictive control algorithm used is its ability to suspend insulin delivery when sensor glucose levels are below 4.4 mmol/l or rapidly declining. As fear of hypoglycaemia is reported as the major barrier to achieving optimal glycaemic control, and the incidence of severe hypoglycaemia is higher during the overnight period,[119] these results suggest a benefit of closed-loop in lowering the risk of otherwise unrecognised and potentially severe nocturnal hypoglycaemia.

After midnight, the improvements in glucose control during closed-loop were even greater, when time in target glucose increased by 41% and time spent above 8.0 mmol/l decreased by 20%. The model predictive control algorithm is an adaptive system whereby current glucose measurements are used to update model parameters such as insulin sensitivity, based on previous insulin infusion rates and carbohydrate intake, resulting in real-time optimisation.[81] As a result, the effectiveness of closed-loop increases with longer duration of use. Optimal glucose control prior to midnight was influenced by the rise in glucose following the evening meal in addition to the prandial insulin bolus administered which was calculated manually.

Significantly, the benefits of closed-loop persisted even after it was discontinued at 08:00. This is similar to the time that patients using overnight closed-loop in the home setting may disconnect from closed-loop on waking, and switch to 'open loop' CSII during the daytime. Between 08:00 and 12:00, time in target glucose during closed-loop visits increased from 22% to 62%, and the time spent in hyperglycaemia was halved. Remarkably, these improvements were seen even with identical insulin infused (subjects' usual CSII regimen) on both visits, and administration of an insulin bolus calculated using subjects' usual bolus calculators for breakfast at 08:00.

Use of closed-loop insulin delivery overnight is a likely intermediate step, prior to fully closed-loop glucose control over 24 hours. Therefore it is encouraging that the improvements overnight were sustained after discontinuation, especially as maintaining glycaemic control during the morning period can be challenging with over 50% of patients with type 1 diabetes experiencing higher glucose levels.[142] In my

study, during conventional CSII visits subjects spent 75% of time in hyperglycaemia after breakfast. This is known as the dawn phenomenon, and may be associated with growth hormone-induced impairment in insulin sensitivity in liver and muscle.

During CSII visits, only 57% of time overnight was spent in normoglycaemia. In other words, nearly half the time was spent outside target glucose range, predominantly in hyperglycaemia. This is an important observation as hyperglycaemia is associated with increased risk of diabetes-related morbidity.[49] Although median time spent below 3.9 mmol/l was only 4%, there were five episodes of hypoglycaemia, in other words almost one episode every two nights. Notably, subjects did not undertake any exercise following the evening meal and were in fact more sedentary in the clinical research facility compared with being at home. One subject experienced two hypoglycaemic events on their CSII visit, one episode occurred whilst awake in the late evening and the second six hours later whilst asleep. Prior hypoglycaemia is known to potentiate the risk of subsequent episodes.[130] No symptoms of hypoglycaemia were experienced for three of the events, two of which occurred overnight at 04:45 and 06:15. This suggests that the incidence of nocturnal hypoglycaemia may be even higher than that reported by patients at home. These observations indicate that even with use of optimised insulin pump regimens in highly motivated patients, current conventional therapies are unable to achieve ideal glycaemic targets.

Importantly, the improvements in overnight glycaemic control with closed-loop were achieved without any requirement for additional insulin infusion. Distinct from conventional CSII, the variable insulin infusion characteristic of closed-loop suggests that the pattern and timing rather than total amount of insulin may be more relevant to optimising insulin delivery (Figure 2.5).

One example of the glucose-responsive insulin delivery characteristic of closed-loop systems was during the postprandial period. Following the evening meal, a lower rate of insulin was infused during closed-loop in order to minimise the risk of delayed postprandial hypoglycaemia associated with miscalculation of prandial insulin or administration of multiple correction boluses resulting in insulin stacking. Even with less basal insulin infused and similar prandial insulin boluses administered, closed-loop achieved a lower peak postprandial plasma glucose (9.0 mmol/l versus 10.2 mmol/l).

Interestingly, the average time to achieve peak glucose following the evening meal was over five hours, in contrast to less than 90 minutes for breakfast. This indicates the wide variation in absorption of ingested carbohydrate between the two meals, which may be related to the size and macronutrient composition. These results may

be useful to clinicians and patients when determining the amount and type of insulin bolus (e.g. simple versus complex) to be administered for meals. Additionally, this information may be valuable in the development of closed-loop algorithms for postprandial glycaemic control.

One of the major strengths of this study was the crossover design where closed-loop insulin delivery was compared with subjects' usual CSII, thus eliminating inter-individual variability in factors such as insulin sensitivity. The randomised order of visits minimised confounding due to adjustment in insulin regimens between visits. Notably, closed-loop insulin delivery was evaluated against maximally optimised CSII which is the best possible insulin replacement currently available to patients with type 1 diabetes.

Importantly, the algorithm used sensor glucose, rather than plasma glucose, to generate the advice on insulin infusion rates, and the algorithm advice was always followed. The study was carried out using commercially available insulin pumps and glucose sensors. A single study pump was used to ensure comparability of insulin delivery between visits. Rapid acting insulin analogue aspart was used in all subjects to enable comparison of plasma insulin measurements. A single sensor was used calibrated according to manufacturers' instructions with no additional calibrations, which is representative of real life. Sensor accuracy measured by the relative difference between paired sensor and reference glucose values was 8.0%, indicating much better performance than previously reported.[16]

Although designed as a pilot feasibility study, the small numbers in addition to the cohort of subjects studied limit applicability of the results to all subjects with type 1 diabetes. Another limitation was the lack of automation of the closed-loop system, and hence the risk of operator error in entering CGM values and changing the insulin pump infusion rates manually every 15 minutes.

Consumption of matched meals on both visits with no snacks or caloric drinks in between the evening meal and breakfast enabled direct comparison of glucose control. However, this may not be representative of a typical evening at home for all patients. Other scenarios such as consuming a bedtime snack will likely have a different effect on glucose excursions. The CSII visit may not have been a true representation of glycaemic control in the home setting, even though subjects continued their usual insulin regimen, as confounding factors including snacks and low intensity physical activity such as housework are likely to have had an effect on glycaemic control. Subjects were blinded to CGM during CSII visits and were hence unable to make any changes based on CGM. This is important as the majority of patients

currently rely on routine fingerprick glucose testing to manage their diabetes.

## 2.7 Conclusion

This pilot study confirmed the feasibility of overnight closed-loop insulin delivery in adults with type 1 diabetes, demonstrating superior glycaemic control, compared with conventional insulin pump therapy. Specifically, time in target glucose ($3.9 - 8.0$ mmol/l) and glycaemic variability were improved with a trend towards reduction in hypoglycaemia. Notably, these benefits were achieved without any additional insulin, and were sustained after discontinuation of closed-loop on waking in the morning.

# Chapter 3

# Closed-loop insulin delivery after evening meal and alcohol

## 3.1 Background

In health, postprandial glycaemic excursions are influenced by the pattern of insulin secretion and its ability to stimulate glucose uptake and suppress endogenous glucose production. In type 1 diabetes, relative insulin deficiency and a lack of meal-induced suppression of glucagon secretion contribute to postprandial hyperglycaemia.[143] The magnitude of glucose excursions following carbohydrate consumption is dependent on various factors including meal size and composition, as well as timing and amount of insulin administered. The resulting hyperglycaemia and accompanying glycaemic variability is associated with an increased risk of diabetes-related complications.[48; 144]

The American Diabetes Association recommends a target postprandial glucose below 10.0 mmol/l.[95] Accurate estimation of carbohydrates to be ingested is a crucial component of diabetes management. Various structured education programmes are available to patients with diabetes, one of which is 'Dose Adjustment For Normal Eating' which has been linked with improved glycaemic control.[145]

Quality, in addition to quantity of carbohydrates consumed, also has an impact on postprandial glycaemic excursions. Glycaemic index, which expresses the blood glucose response after eating a standard amount of food relative to the response after consuming the same amount of carbohydrate as glucose, has been shown to be a stronger predictor of postprandial glucose and insulin responses compared with carbohydrate quantity alone.[146] Consumption of a low glycaemic index meal may be

associated with lower glucose levels.[147] A meta-analysis of 14 randomised studies found a small but significant improvement in HbA1c (0.43%) for diets with a lower glycaemic index.[148]

Prandial insulin boluses may be estimated using a pump bolus wizard or similar calculator, which is individualised with patients' insulin sensitivity and insulin to carbohydrate ratios, and requires entry of results of fingerprick glucose testing and grams of carbohydrate to be consumed. Manual calculation using individualised insulin to carbohydrate ratios may be more difficult and time consuming. For some patients, the complexity of such tasks may lead to incorrect calculation or empirical estimation, which can result in mismatch between carbohydrates and insulin and subsequent increased risk of hyper- or hypoglycaemia. Delivery of the insulin bolus itself may be overlooked: a study in Swedish adolescents found that over a third had missed more than 15% of boluses, which was correlated with worse glycaemic control.[149]

One of the major limitations of subcutaneous insulin delivery is the delay in time to peak blood glucose lowering effect which may be $90-120$ minutes with the currently available rapid acting insulin analogues.[93] These delays result in slower glucose disposal with subsequent postprandial hyperglycaemia. This may prompt inadvertent administration of correction boluses and insulin stacking, thus increasing the risk of delayed hypoglycaemia. Optimising timing of insulin bolus delivery may improve postprandial control. Administration of rapid acting insulin as a simple bolus 15 to 20 minutes prior to eating has been shown to result in lower peak glucose and greater time in target during conventional pump therapy, compared with delivery at the beginning or after a meal.[150; 151] There are several novel approaches under development targeting improved insulin pharmacokinetics, ranging from modifications in insulin formulations to enhancement of the mode of delivery. These have been reviewed in Section 1.4.3.

Alcohol plays a significant role in many social situations. Moderate alcohol consumption in healthy individuals has been shown to be associated with lower postprandial glucose levels, improved insulin sensitivity and a 30% lower incidence of type 2 diabetes.[152; 153] In patients with type 1 diabetes, alcohol in moderation has been shown to have a beneficial effect on microvascular complications, including neuropathy and retinopathy.[154] However, it is also associated with a significantly higher risk of delayed or reactive hypoglycaemia.[155] The main mechanism is inhibition of hepatic glucose production, which usually accounts for a significant proportion of basal glucose production during hypoglycaemia in type 1 diabetes.

Alcohol is metabolised in the liver by oxidation to acetaldehyde and acetate. This process is dependent on the cofactor nicotinamide adenine dinucleotide, excess consumption of which results in lower levels available for gluconeogenesis. Another reason for hypoglycaemia may be administration of correction doses of insulin to counter the initial rise in glucose levels that occurs when drinking alcohol. An immediate and prolonged hypoglycaemic effect of alcohol was observed using CGM following the ingestion of vodka or placebo in 16 adults with type 1 diabetes during free-living.[156]

Alcohol can result in impairment of the counter-regulatory response to hypoglycaemia. Clamp studies performed during hypoglycaemia with concurrent alcohol consumption in 17 subjects with type 1 diabetes demonstrated an attenuated response to growth hormone with no differences in glucagon, adrenaline and cortisol levels.[157] The release of growth hormone in the counter-regulatory response to hypoglycaemia is especially important for patients with type 1 diabetes, as the response to adrenaline is attenuated and glucagon secretion is absent. An inpatient study in six young men with type 1 diabetes demonstrated lower fasting and postprandial glucose levels with increased symptomatic hypoglycaemia the morning after an evening of drinking alcohol.[158] Overnight secretion of growth hormone was also reduced.

In addition to the direct effects on glycaemic control, alcohol can impair judgement which may result in lower self-management of diabetes, such as failing to detect and treat a hypoglycaemic episode. Furthermore, hypoglycaemic symptoms may be misinterpreted by others as alcohol intoxication. Alcohol consumption may exaggerate the cognitive impairment that occurs with more severe hypoglycaemia. This was demonstrated during clamp studies in 17 subjects with type 1 diabetes, where consumption of vodka resulted in impaired reaction times and cognitive performance independent of glucose concentration.[159] Induction of hypoglycaemia in combination with alcohol led to further deterioration in all aspects of cognitive testing. Slower reaction times, blunted hand tremor and increased sweating were demonstrated in a study in healthy subjects and patients with type 1 diabetes, during hypoglycaemia following moderate alcohol consumption.[160] Notably, only two out of the 15 participants were aware of being hypoglycaemic after drinking alcohol compared with 11 after consuming the placebo drink.

There is high inter-individual variability in ethanol pharmacokinetics, influenced by factors such as age, gender and ethnicity. In addition, intra-individual differences, including consumption of food and variation in gastrointestinal function, specifically gastric emptying, intestinal transit time, portal blood flow and hepatic first pass ex-

traction have variable effects on the metabolic response to alcohol.[161] A study of ethanol ingestion before or after an evening meal in healthy young males demonstrated higher intra- and inter-subject variability in the fed state.[162] Other factors include the strength, type and quantity of ethanol, and length of time spent drinking. The influence of these multiple factors makes it challenging for people with type 1 diabetes to maintain normal glycaemic levels when drinking alcohol. Consumption of alcohol without food can result in more severe hypoglycaemia due to alcohol-induced suppression of gluconeogenesis, which is the main source of glucose in the fasting state, in addition to depleted liver glycogen stores.[155]

Guidelines for alcohol consumption in patients with diabetes are similar to those of the general population: the American Diabetes Association recommends a daily maximum of one drink for women and two for men, while Diabetes UK advises a daily limit of two units for women and three units for men. There is minimal evidence regarding optimal insulin regimens when drinking alcohol. As such, patients make adjustments based on personal experience and anecdotal evidence. A survey of college students with type 1 diabetes found that the majority made no changes to their diabetes regimen of students when drinking alcohol.[163]

## 3.2 Rationale

Conventional insulin pump therapy relies on pre-programmed basal infusion rates and complex calculations for prandial insulin boluses, based on results of fingerprick glucose testing and estimation of quantity of carbohydrate to be consumed. Incorrect estimation, such as of foods not normally consumed, may lead to mismatch between insulin and carbohydrates resulting in fluctuating glucose levels. Additionally, bolus calculations are not able to take into account concurrent influences such as drinking alcohol or physical activity which are associated with an increased risk of hypoglycaemia. A closed-loop system linking continuous glucose monitoring with insulin delivery using a model predictive control algorithm may provide safer glucose control following such situations. An algorithm incorporating meal announcement may help overcome the delays associated with absorption of subcutaneously delivered insulin and appearance of meal-related glucose in the bloodstream.

The feasibility study described in Chapter 2 confirmed the safety and efficacy of overnight closed-loop insulin delivery overnight following a medium-sized evening meal similar to that consumed at home. Several other common scenarios faced by patients with type 1 diabetes in daily life may provide a greater challenge to gly-

caemic control. These include eating a larger meal at a restaurant which may result in postprandial hyperglycaemia, and drinking alcohol which is associated with a risk of delayed hypoglycaemia.

## 3.3 Aim

The aim of this study was to evaluate the efficacy and safety of overnight closed-loop insulin delivery, in particular the frequency of nocturnal or early morning hypoglycaemia, following an evening of drinking alcohol accompanying a large meal, compared with conventional insulin pump therapy (CSII), in adults with type 1 diabetes in a controlled setting.

## 3.4 Methods

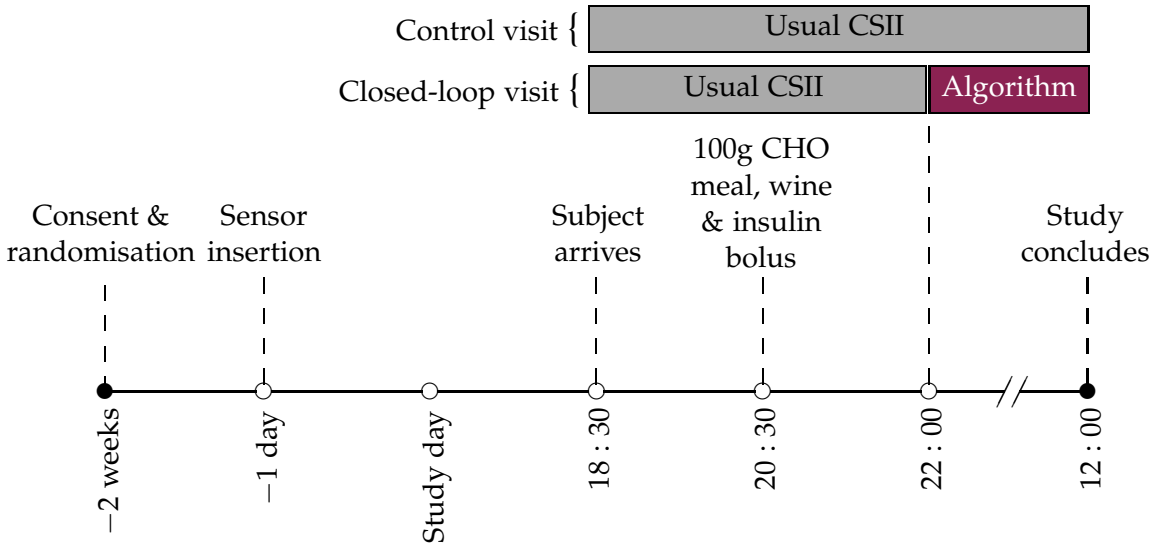
### 3.4.1 Participants

Twelve new participants, different from those enrolled in the feasibility study, were recruited from the adult diabetes outpatient clinic at Addenbrooke's Hospital, Cambridge, UK. Inclusion and exclusion criteria were the same as those applied in the feasibility study. Additional exclusion criteria included current pregnancy or breastfeeding, poorly controlled diabetes defined by an HbA1c $\geq$ 10%, total daily insulin dose $\geq$ 1.4 U/kg, and intolerance or inability to consume the necessary quantity of alcohol as per the study design. The study protocol was approved by the Cambridgeshire Research Ethics Committee, and carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant.

### 3.4.2 Study design

The study had a randomised crossover design similar to that of the feasibility study described in Section 2.4.2. The timeline of procedures is shown in Figure 3.1. There was no period of optimisation of insulin therapy prior to study commencement. Subjects attended for a closed-loop visit, which involved inputs of glucose concentration and insulin infusion rates into a computer programme and a manual pump setting following advice of the algorithm output, and a control (usual CSII) visit. A glucose sensor (blinded mode) was inserted one to two days prior to each study visit, and subjects were asked to arrive at the clinical research facility at 18:30. Blood sampling

Figure 3.1: Timeline of study procedures




**Notes:** Closed-loop and control (CSII) interventions were carried out in random order, with a one to three week interval between visits.

for glucose, insulin and ethanol commenced at 19:30 and continued until midday the following day.

Between 20:30 and 22:00, subjects consumed a 100g carbohydrate mixed meal (50% carbohydrate, 30% fat, 20% protein) accompanied by 0.75g ethanol per kg body weight dry white wine (Chenin Blanc, South Africa, 13% alcohol volume). All meals were prepared in advance on site in the hospital kitchen. The size of the meal and quantity of alcohol consumed were identical on both study visits. The volume of alcohol, which was based on a previous study evaluating wine consumption in young men with type 1 diabetes,[158] was calculated as:

$$\text{Volume (ml)} = \frac{\text{Units}}{\text{Alcohol by volume (\%)}} \times 1,000$$

where

$$\begin{aligned} \text{Units} &= \frac{\text{Total quantity of ethanol (g)}}{8\text{g}}; \text{ and} \\ \text{Total ethanol (g)} &= 0.75 \times \text{Body weight (kg)} \end{aligned}$$

For example, for a 70-kg subject:

$$\begin{aligned} \text{Total ethanol} &= 0.75 \times 70 = 52.5\text{g} \\ \text{Units} &= \frac{52.5}{8} = 6.6\text{U} \\ \text{Volume} &= \frac{6.6}{13} \times 1,000 = 505\text{ml} \end{aligned}$$

An insulin bolus, calculated using the subjects' usual bolus wizard calculator, was administered concurrently. At 22:00, closed-loop was initiated and maintained until 12:00 the following day. On the control night, subjects continued their usual insulin pump regimen.

Subjects were able to relax in the clinical research facility while having their meal and wine, and went to sleep according to their preference. They were not permitted any other food or caloric drinks until study completion at midday the following day, thus simulating a late evening out and sleeping until lunchtime the next day. In comparison with the feasibility study, the evening meal had a higher carbohydrate content, more similar to a meal consumed when eating out at a pub or restaurant.

Episodes of hypoglycaemia were treated if the subject felt symptomatic with a confirmed plasma glucose $< 3.0$ mmol/l. Plasma glucose below 2.0 mmol/l resulted in discontinuation of the study visit.

#### 3.4.2.1 Randomisation and blinding

A block randomisation procedure allocated subjects to the order in which they completed their algorithm and control nights. Subjects were blinded to CGM and plasma glucose values on both visits. Investigators were not blinded to plasma glucose values, which were measured in real-time, for safety reasons.

#### 3.4.2.2 Closed-loop visit

The closed-loop system was similar to that used in the feasibility study, but was initiated at 22:00 (closer to bedtime) and continued until 12:00 the following day (total of 14 hours). The start time was chosen to mimic returning home late and subsequently commencing closed-loop at a later time.

- **Continuous glucose sensor.** The next generation FreeStyle Navigator CGM (Abbott Diabetes Care, Alameda, CA, USA) was used, which could be calibrated and ready for use one hour after the sensor was *in situ* (Figure 1.1).

- **Model Predictive Control (MPC) algorithm.** Versions 0.02.14.0 to 0.02.18.0 of the MPC algorithm designed at the University of Cambridge were used.
- **Study pump.** The Deltec Cozmo (Smiths Medical, St Paul, MN, USA) pump was used on all study visits, and connected to an established infusion site. The rapid acting insulin analogue aspart (Novo Nordisk, Bagsvaerd, Denmark) was used for all study visits.

#### 3.4.2.3 CSII visit

On CSII visits, subjects continued their usual insulin pump regimen. This included setting temporary basal rates and/or reducing the insulin bolus taken for the evening meal as per their usual practice when drinking alcohol.

### 3.4.3 Measurements

All samples of whole blood were immediately centrifuged and separated. Plasma glucose was measured in real-time on a YSI 2300 STAT Plus analyser (YSI Ltd, Fleet, UK). Plasma samples of insulin were stored at $-80\,^{\circ}$C and ethanol on dry ice, for later analysis. Plasma insulin was measured using an immunochemiluminometric assay (Invitron Ltd, Monmouth, UK). Plasma ethanol was determined using the ethyl alcohol method (Dade Behring Inc, Atterbury, Milton Keynes, UK). At a mean of 6.6 mmol/l, the intra-assay and inter-assay coefficient of variation were 2.4% and 5.7%, respectively.

### 3.4.4 Statistical analysis

#### 3.4.4.1 Power calculation

Similar to the 'Feasibility' study described in Chapter 2, the power calculation was based on the results of evaluation of closed-loop in children,[104] as the results from the first study in adults were not available at the time of designing this study.

#### 3.4.4.2 Efficacy endpoints

The primary outcome measure was proportion of time spent with plasma glucose in target range ($3.9 - 8.0$ mmol/l) between 22:00 and 12:00. The secondary outcome measures were identical to those measured in the feasiblity study. In addition, peak plasma ethanol concentration and area under the ethanol concentration curve (AUC)

were calculated to verify similar metabolism of the alcohol consumed on closed-loop and CSII visits. Secondary outcomes were calculated using plasma and sensor (CGM) glucose, for the following time periods:

- **Overall period (22:00-12:00).** On closed-loop visits, the 'overall period' was defined as the interval from commencement of the algorithm at 22:00 until discontinuation at 12:00 the following day. On CSII visits, this was defined as the corresponding time period when subjects continued their usual CSII regimen.
- **Overnight period (00:00-08:00).** On closed-loop visits, the 'overnight period' was defined from midnight to 08:00. On CSII visits, this was the corresponding period in time when subjects continued their usual CSII regimen. This period was chosen as it enabled evaluation of glycaemic control at night time specifically.
- **Latter period (03:00-12:00).** On closed-loop visits, the 'latter period' was defined as the period five hours after commencement of the algorithm until discontinuation at 12:00. This period was chosen as it enabled comparison with the corresponding period in the feasibility study five hours after the algorithm was started at 19:00. On CSII visits, this was the corresponding period in time when subjects continued their usual CSII regimen.
- **Morning period (08:00-12:00)** On closed-loop visits the 'morning period' was defined from 08:00 until end of study at 12:00. On CSII visits, this was the corresponding period in time when subjects continued their usual CSII regimen. This period enabled evaluation of morning glycaemic control, specifically risk of delayed hypoglycaemia.

Statistical analyses were carried out as described in Section 2.4.4, using SPSS, Version 15 (SPSS Inc, Chicago, IL, USA).

The AUC of plasma ethanol was determined by calculating the sum of the average plasma ethanol concentrations at each time period (i.e. average plasma ethanol $\times$ time). The intra-individual variability in peak plasma ethanol and AUC ethanol were analysed by calculating the coefficient of variation of the difference between first and second study visits. The inter-individual coefficient of variation of peak plasma ethanol and AUC ethanol was determined from the mean and standard deviation of all study visits. Coefficient of variation, defined as the standard deviation expressed as a percentage of the mean, measures the dispersion of data around the mean.

Table 3.1: Demographics of 12 participants

| Characteristic | Number of subjects | Mean | Standard deviation |
|---|---|---|---|
| Sex (male/female) | 5/7 | | |
| Age (years) | | 37.2 | 9.9 |
| Weight (kg) | | 78.2 | 18.5 |
| Body mass index (kg/m$^2$) | | 26.8 | 4.2 |
| HbA1c (%) | | 7.8 | 0.7 |
| Duration of diabetes (years) | | 19.7 | 9.7 |
| Duration on pump (years) | | 1.9 | 2.5 |
| Insulin used (aspart/lispro) | 6/6 | | |
| Total daily insulin (U) | | 52.6 | 19.2 |
| Total daily basal (U) | | 20.6 | 8.2 |
| Total daily bolus (U) | | 32.1 | 12.5 |
| Total daily insulin/kg (U) | | 0.7 | 0.1 |
| Volume of wine consumed (mls) | | 564 | 133 |

Primary and secondary outcomes were calculated for all 12 subjects, except for the time periods 03:00-12:00 and 08:00-12:00, which analysed only 11 subjects as one subject's CSII study visit was terminated prematurely at 02:00 due to plasma glucose measurement below 2.0 mmol/l. This subjects' data was included in the analyses of the overall and 00:00-08:00 time periods without extrapolation of missing data. The postprandial period was defined from 21:00 until midnight, as subjects had a longer time frame over which the meal and alcohol was consumed.

## 3.5 Results

Between September and December 2009, 41 patients attending the adult diabetes outpatient clinic at Addenbrooke's Hospital were screened. Those patients that were eligible for participation were sent letters of invitation to take part. Fourteen new subjects were enrolled, two of which withdrew from proceeding prior to consent, with 12 completing both study visits.

The demographics of the subjects at study entry are summarised in Table 3.1. Mean duration of type 1 diabetes ranged from 5.7 to 38.6 years and time on pump therapy from 0.3 to 9.3 years. The average time between study visits was $12 \pm 6$ days.

Table 3.2: Time spent with plasma glucose in target during closed-loop and CSII, for overall, overnight, latter and morning periods

| | | 3.9 < Plasma glucose ≤ 8.0 mmol/l (%) | |
|---|---|---|---|
| Period | | Median | Interquartile range |
| Overall (22:00-12:00)[a] | CL | 70 | (60,87) |
| | CSII | 46 | (29,65) |
| | P-value | 0.012* | |
| Overnight (00:00-08:00)[a] | CL | 61 | (44,81) |
| | CSII | 53 | (30,78) |
| | P-value | 0.182 | |
| Latter (03:00-12:00)[b] | CL | 88 | (65,96) |
| | CSII | 48 | (15,75) |
| | P-value | 0.016* | |
| Morning (08:00-12:00)[b] | CL | 100 | (100,100) |
| | CSII | 40 | (0,98) |
| | P-value | 0.008* | |

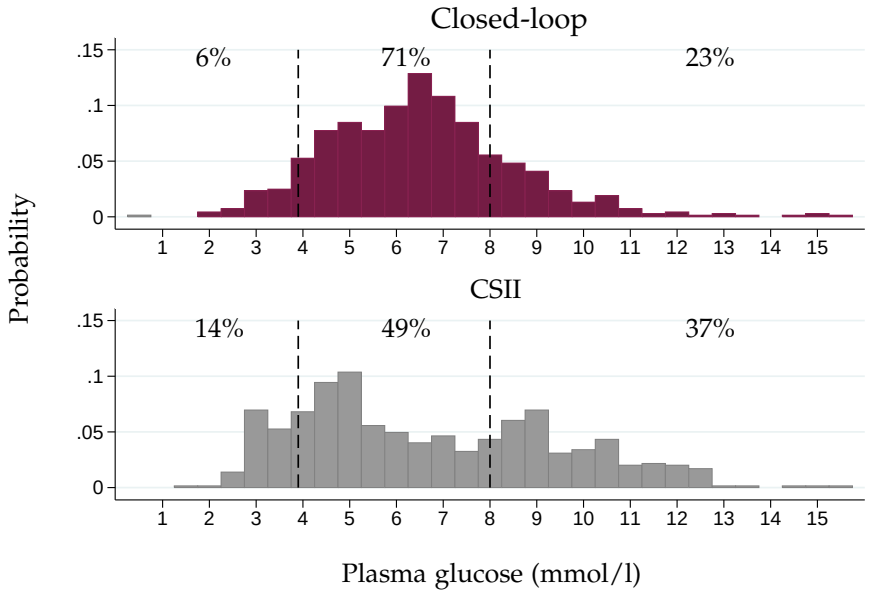
**Notes:** [a] calculations based on 12 subjects; [b] calculations based on 11 subjects. * denotes statistical significance at the 5% level.

### 3.5.1 Primary outcome

During the overall study period (22:00 to 12:00), the proportion of time spent with plasma glucose in target range ($3.9 - 8.0$ mmol/l) increased from 46% during conventional CSII to 70% during closed-loop; $p = 0.012$ (Table 3.2).

This is illustrated in Figure 3.2 by a higher probability of plasma glucose being in target range ($3.9 - 8.0$ mmol/l) during closed-loop (71%) compared with CSII (49%), in addition to an almost halving of values in the hyperglycaemic and hypoglycaemic ranges.

Figure 3.2: Distribution of plasma glucose during closed-loop and CSII




**Notes**: Percent values denote proportion of plasma glucose values below, within and above target (3.9 – 8.0 mmol/l), during closed-loop and CSII.

### 3.5.2 Secondary outcomes

#### 3.5.2.1 Average glucose and variability

Secondary analysis of individual time periods showed a greater proportion of time spent with glucose in target range during the latter (88% versus 48%) and morning (100% versus 40%) periods under closed-loop insulin delivery, compared with the overnight period (61% versus 53%), suggesting improved performance of closed-loop with longer duration of use (Table 3.2).

There was no difference in the mean plasma glucose overall between closed-loop and CSII; 6.8 mmol/l versus 6.9 mmol/l, $p = 0.672$ (Table 3.3).

Closed-loop lowered the standard deviation of glucose from 2.3 mmol/l to 1.7 mmol/l ($p = 0.041$). Glucose variability is illustrated by the interquartile range in Figure 3.3, which was similarly increased during closed-loop and CSII in the first half of the night, most likely related to the effect of the large meal and wine on

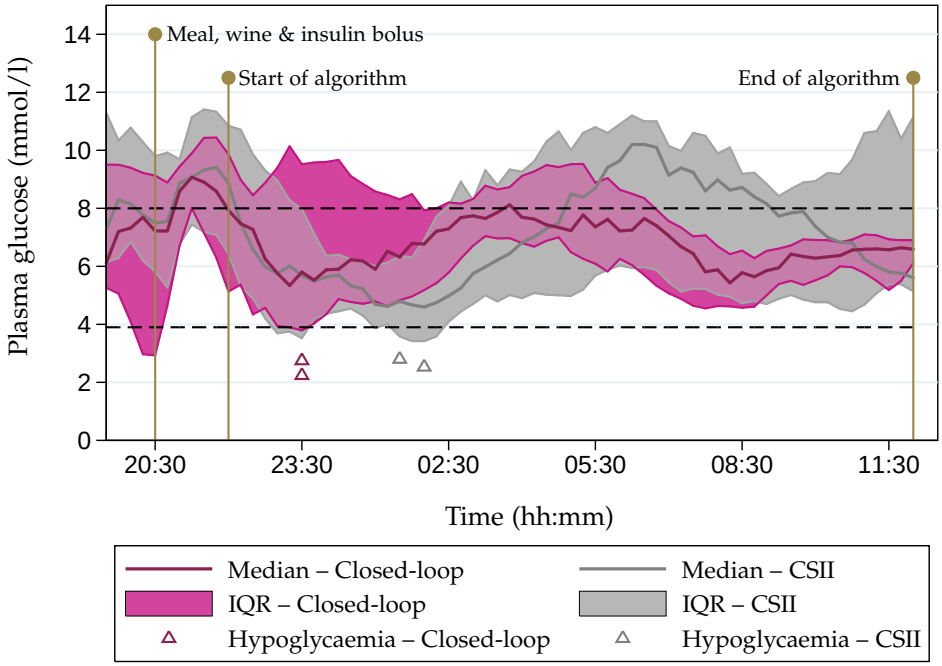
Table 3.3: Plasma glucose outcomes during closed-loop and CSII, for overall, overnight, latter and morning periods

| | Overall (22:00-12:00)[a] | | | Overnight 00:00-08:00[a] | | | Latter 03:00-12:00[b] | | | Morning 08:00-12:00[b] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CL | CSII | P-value | CL | CSII | P-value | CL | CSII | P-value | CL | CSII | P-value |
| Plasma glucose at start of CL (mmol/l) | 8.1 ± 3.4 | 9.4 ± 3.7 | 0.349 | — | — | — | — | — | — | — | — | — |
| Mean plasma glucose (mmol/l) | 6.8 ± 0.8 | 6.9 ± 1.5 | 0.672 | 7.1 ± 1.0 | 6.8 ± 2.0 | 0.587 | 6.7 ± 0.6 | 7.6 ± 2.5 | 0.261 | 6.0 ± 0.6 | 7.3 ± 2.6 | 0.120 |
| Standard deviation of plasma glucose (mmol/l) | 1.7 (1.3,2.0) | 2.3 (1.8,2.9) | 0.041* | 1.7 (1.1,1.7) | 1.4 (0.9,2.2) | 0.638 | 1.3 (1.1,1.8) | 1.0 (0.6,1.8) | 0.534 | 0.7 (0.5,1.0) | 0.5 (0.4,1.4) | 0.722 |
| 3.9 < Plasma glucose ≤ 8.0 mmol/l (%) | 70 (60,87) | 46 (29,65) | 0.012* | 61 (44,81) | 53 (30,78) | 0.182 | 88 (65,96) | 48 (15,75) | 0.016* | 100 (100,100) | 40 (0,98) | 0.008* |
| Plasma glucose <3.0 mmol/l (%) | 0 (0,2) | 0 (0,2) | 0.600 | 0 (0,0) | 0 (0,3) | 0.273 | 0 (0,0) | 0 (0,0) | 1.000 | 0 (0,0) | 0 (0,0) | 1.000 |
| Plasma glucose ≤ 3.9 mmol/l (%) | 3 (0,10) | 14 (0,26) | 0.093 | 0 (0,5) | 6 (0,25) | 0.123 | 0 (0,1) | 0 (0,21) | 0.138 | 0 (0,0) | 0 (0,3) | 0.273 |
| Plasma glucose > 8.0 mmol/l (%) | 24 (9,38) | 35 (12,59) | 0.041* | 31 (12,49) | 26 (0,70) | 0.875 | 9 (4,35) | 52 (0,85) | 0.075 | 0 (0,0) | 41 (0,100) | 0.012* |
| Low blood glucose index | 1.1 (0.6,1.8) | 2.8 (0.4,4.7) | 0.099 | 0.5 (0.2,1.4) | 2.3 (0.3,5.2) | 0.117 | 0.7 (0.1,1.2) | 0.3 (0,4.1) | 0.859 | 0.7 (0.1,1.9) | 0.1 (0.0,3.2) | 0.859 |
| High blood glucose index | 1.3 (0.5,2.4) | 2.5 (1.6,4.0) | 0.060 | 1.6 (0.7,3.0) | 1.7 (0.0,5.2) | 0.388 | 0.6 (0.5,2.2) | 3.8 (0.0,5.8) | 0.050* | 0.2 (0.1,0.3) | 2.3 (0.0,5.9) | 0.028* |

**Notes**: Data are mean ± standard deviation or median (interquartile range). [a] Calculations based on 12 subjects; [b] calculations based on 11 subjects.

* Denotes statistical significance at the 5% level.

Figure 3.3: Plasma glucose profiles during closed-loop and CSII




glucose levels. From approximately 03:00 during closed-loop, the interquartile range was much narrower compared with CSII.

Median plasma glucose profiles were similar between interventions following the evening meal and alcohol, remaining in target range during closed-loop throughout the study (Figure 3.3). In comparison during CSII, median glucose levels rose above target from approximately 05:00 until after 09:00. Additionally, between 00:00 and 04:00 the median plasma glucose on CSII visits was at the lower end of target range suggesting a higher risk of nocturnal hypoglycaemia compared with closed-loop when plasma glucose remained between $6 - 8$ mmol/l.

Secondary outcomes calculated using sensor glucose are summarised in Table 3.4. Closed-loop increased the overall time spent with sensor glucose values in target range by 33% ($p = 0.015$), and reduced variability (glucose standard deviation 1.5 mmol/l versus 2.7 mmol/l; $p = 0.050$).

Individual plasma and sensor glucose profiles for each subjects' closed-loop and CSII visits are provided in Appendix A.

Table 3.4: Sensor glucose outcomes during closed-loop and CSII, for overall, overnight, latter and morning periods

| | Overall (22:00-12:00)[a] | | | Overnight 00:00-08:00[a] | | | Latter 03:00-12:00[b] | | | Morning 08:00-12:00[b] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CL | CSII | P-value | CL | CSII | P-value | CL | CSII | P-value | CL | CSII | P-value |
| Sensor glucose at start of CL (mmol/l) | 9.9 ± 3.8 | 10.5 ± 3.7 | 0.672 | — | — | — | — | — | — | — | — | — |
| Mean plasma glucose (mmol/l) | 7.3 ± 1.3 | 7.5 ± 2.0 | 0.701 | 7.5 ± 1.5 | 7.2 ± 2.6 | 0.700 | 7.1 ± 0.9 | 8.1 ± 3.0 | 0.249 | 6.5 ± 0.4 | 7.8 ± 3.0 | 0.141 |
| Standard deviation of sensor glucose (mmol/l) | 1.5 (1.3,2.4) | 2.7 (1.9,3.0) | 0.050* | 1.5 (1.1,1.9) | 1.7 (1.0,2.3) | 0.754 | 1.2 (0.9,1.5) | 1.1 (0.7,1.9) | 0.594 | 0.8 (0.5,1.1) | 0.6 (0.4,1.2) | 0.859 |
| $3.9 <$ Sensor glucose $\leq 8.0$ mmol/l (%) | 73 (49,84) | 40 (26,62) | 0.015* | 67 (31,82) | 50 (21,76) | 0.158 | 79 (58,95) | 46 (22,77) | 0.010* | 100 (85,100) | 60 (0,100) | 0.012* |
| Sensor glucose $<3.0$ mmol/l (%) | 0 (0,0) | 0 (0,2) | 0.225 | 0 (0,0) | 0 (0,4) | 0.225 | 0 (0,0) | 0 (0,0) | 0.180 | 0 (0,0) | 0 (0,0) | 1.000 |
| Sensor glucose $\leq 3.9$ mmol/l (%) | 0 (0,4) | 5 (0,26) | 0.093 | 0 (0,1) | 9 (0,28) | 0.050* | 0 (0,0) | 0 (0,10) | 0.138 | 0 (0,0) | 0 (0,0) | 0.655 |
| Sensor glucose $> 8.0$ mmol/l (%) | 27 (9,50) | 43 (14,65) | 0.084 | 33 (10,69) | 35 (0,73) | 0.695 | 16 (2,42) | 53 (0,78) | 0.050* | 0 (0,7) | 37 (0,100) | 0.018* |
| Low blood glucose index | 0.6 (0.1,1.1) | 1.7 (0.3,5.5) | 0.060 | 0.3 (0,1.5) | 2.4 (0.1,6.2) | 0.050* | 0.2 (0.1,0.4) | 0.4 (0,3.0) | 0.286 | 0.2 (0.2,0.4) | 0.0 (0.0,1.7) | 0.646 |
| High blood glucose index | 1.7 (0.6,4.1) | 2.6 (2.1,7.1) | 0.099 | 1.9 (0.6,5.3) | 2.0 (0.1,7.9) | 0.583 | 1.3 (0.3,2.6) | 3.6 (0.0,10.0) | 0.131 | 0.3 (0.1,0.7) | 2.5 (0.0,8.1) | 0.041* |

**Notes**: Data are mean ± standard deviation or median (interquartile range). [a] Calculations based on 12 subjects; [b] calculations based on 11 subjects.

* Denotes statistical significance at the 5% level.

#### 3.5.2.2 Hypoglycaemia

The proportion of time spent in hypoglycaemia ($< 3.9$ mmol) was 3% during closed-loop compared with 14% during CSII although this difference was not significant; $p = 0.093$ (Table 3.3). Using sensor glucose outcomes (Table 3.4), closed-loop reduced the time spent in hypoglycaemia after midnight from 9% to 0% ($p = 0.050$) and the low blood glucose index from 2.4 to 0.3 ($p = 0.050$). The frequency of hypoglycaemia on both closed-loop and CSII visits was low overall, with only seven plasma glucose measurements below 3.0 mmol/l during closed-loop and 11 on CSII (Table 3.5). After midnight, there were two plasma glucose values below 3.0 mmol/l on closed-loop and seven on CSII.

There were four hypoglycaemic events overall, defined as plasma glucose $< 3.0$ mmol/l: two during closed-loop and two during CSII visits (Table 3.6). There was no requirement for intravenous dextrose on any episode. The events during closed-loop occurred within three hours of consumption of the meal and wine and were likely related to the prandial bolus administered. They were both associated with symptoms and resolved with 15g of quick-acting carbohydrate as Lucozade Energy drink (GlaxoSmithKline, UK) or orange juice. The hypoglycaemic episodes on CSII visits occurred after midnight and were both asymptomatic. One of these resulted in early termination of the subject's study visit at 02:00, as per study protocol, as plasma glucose nadir was $< 2.0$ mmol/l. This subject had a large bolus of 24U for the evening meal which may have contributed to the hypoglycaemia. Of note, the bolus was calculated using their usual bolus wizard and was identical to that administered for the evening meal on the closed-loop visit.

#### 3.5.2.3 Hyperglycaemia

Closed-loop lowered the overall time spent with plasma glucose above 8.0 mmol/l from 35% to 24%; $p = 0.041$ (Table 3.3). After 08:00, there were no plasma glucose measurements above 8.0 mmol/l during closed-loop. There was a significant reduction in the high blood glucose index, measuring duration and extent of hyperglycaemia, during closed-loop from 03:00. A similar improvement in hyperglycaemia during closed-loop was seen using sensor glucose outcomes, with significant reduction after 03:00 from 53% to 16%; $p = 0.050$ (Table 3.4).

Table 3.5: Plasma glucose values in hypoglycaemic range during closed-loop and CSII for overall (19:00-08:00), overnight (00:00-08:00), latter (03:00-12:00) and morning (08:00-12:00) periods

| | Overall | | | | Overnight | | | | Latter | | | | Morning | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Plasma glucose | CL | | CSII | | CL | | CSII | | CL | | CSII | | CL | | CSII | |
| (mmol/l) | $n$ | % | $n$ | % | $n$ | % | $n$ | % | $n$ | % | $n$ | % | $n$ | % | $n$ | % |
| $< 2.00$ | 0 | 0.0 | 1 | 0.0 | 0 | 0.0 | 1 | 0.3 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| $2.00 - 2.49$ | 3 | 0.4 | 1 | 0.2 | 0 | 0.0 | 1 | 0.3 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| $2.50 - 2.99$ | 4 | 0.6 | 9 | 1.4 | 2 | 1.0 | 5 | 1.4 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| $3.00 - 3.49$ | 17 | 2.5 | 44 | 6.8 | 8 | 2.0 | 24 | 6.6 | 3 | 1.0 | 19 | 4.7 | 2 | 1.0 | 8 | 4.3 |
| $3.50 - 3.89$ | 15 | 2.2 | 25 | 3.9 | 9 | 2.3 | 11 | 3.0 | 7 | 1.6 | 16 | 3.9 | 2 | 1.0 | 9 | 4.8 |
| Total $< 3.9$ | 39 | 5.7 | 80 | 12.4 | 19 | 4.9 | 42 | 11.6 | 10 | 2.3 | 35 | 8.6 | 4 | 2.0 | 17 | 9.1 |
| Total $(N)$ | 684 | | 646 | | 384 | | 363 | | 444 | | 407 | | 204 | | 187 | |

**Notes:** $N$ denotes total number of plasma glucose values, and $n$ denotes number of plasma glucose values $< 3.9$ mmol/l, within the specified period. $N_{\text{CSII}} < N_{\text{CL}}$ as one subject's CSII visit was terminated early due to hypoglycaemia $< 2.0$ mmol/l.

Table 3.6: Detail of all hypoglycaemia episodes

| Study visit | Subject ID | Plasma glu (mmol/l) | Time | Duration (min) | Symptoms (Yes/No) | Treated (Yes/No) | CHO (g) |
|---|---|---|---|---|---|---|---|
| CL | 4 | 2.75 | 23:30 | 30 | Y | Y | 15 |
| CL | 11 | 2.24 | 23:30 | 30 | Y | Y | 15 |
| CSII | 3 | 2.80 | 01:30 | 45 | N | N | 0 |
| CSII | 6 | 2.53[a] | 02:00 | 45 | N | Y | 30 |

**Notes:** CHO denotes rescue carbohydrates consumed. [a]Plasma glucose nadir of 1.89 mmol/l resulted in termination of study visit.

#### 3.5.2.4 Insulin

There was no difference in the hourly insulin infusion rate between closed-loop and CSII visits; 0.8 U/h versus 0.9 U/h, $p = 0.327$ (Table 3.7). Insulin infusion rates ranged from $0 - 3.3$ U/h on closed-loop and from $0.2 - 2.5$ U/h on CSII study visits. The greater variability in infusion rates during closed-loop is illustrated by the wider and changing interquartile range shown in Figure 3.4, compared with CSII. Measured plasma insulin concentration was similar between visits; 139 pmol/l versus 128 pmol/l, $p = 0.272$ (Table 3.7). Figure 3.5 shows the plasma insulin profiles during both interventions; the median trends were comparable overall.

#### 3.5.2.5 Meals and postprandial period

Participants chose a standardised 100g carbohydrate meal of their preference and consumed the identical meal on both study visits. The first four subjects' meals were slightly larger ($107 - 118g$), although these were matched on both study visits. The average quantity of carbohydrates consumed for the evening meal overall was 105g (Table 3.8).

The average prandial insulin bolus administered was 11U on closed-loop and 11.7U on CSII visits. As white wine has minimal carbohydrate content (0.82g/100ml), the alcohol consumed was not considered in the calculation of the prandial bolus taken for the evening meal.[164] Two subjects administered a dual wave (extended) bolus of insulin, according to their usual practice to cover the larger meal to be consumed (Table 3.8). One subject had a very large prandial bolus of 24U on both their study visits, but this was consistent with their standard insulin to carbohydrate ratio calculations. The prandial bolus was administered within 20 minutes of commencing

Table 3.7: Summary of plasma insulin and insulin infused during closed-loop and CSII, for overall, overnight, latter, morning and postprandial periods

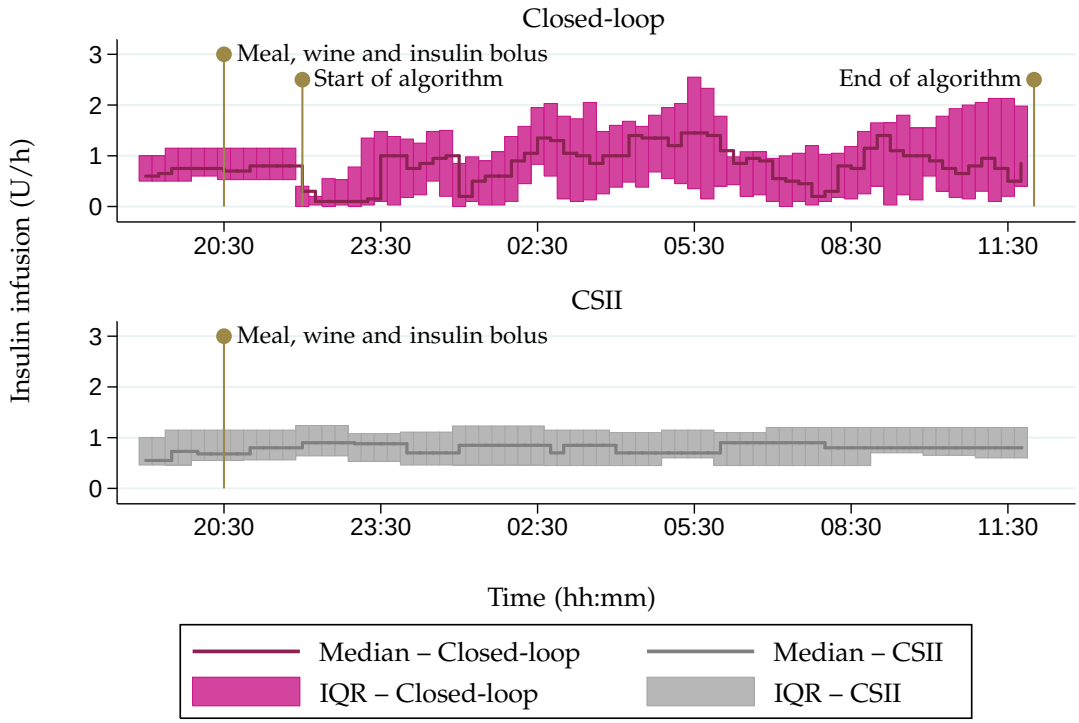
| | | Plasma insulin (pmol/l) | | Insulin infusion (U/h) | | Total insulin (U) | |
|---|---|---|---|---|---|---|---|
| Period | | Median | IQR | Median | IQR | Median | IQR |
| Overall (22:00-12:00)[a] | CL | 139 | (98,177) | 0.8 | (0.6,1.2) | 11.9 | (8.4,17.0) |
| | CSII | 128 | (103,212) | 0.9 | (0.6,1.1) | 12.3 | (8.2,16.0) |
| | P-value | 0.272 | | 0.327 | | 0.711 | |
| Overnight (00:00-08:00)[a] | CL | 134 | (70,150) | 1.0 | (0.6,1.2) | 7.9 | (5.1,9.8) |
| | CSII | 102 | (77,157) | 0.9 | (0.6,1.1) | 6.8 | (4.8,9.0) |
| | P-value | 0.754 | | 0.114 | | 0.071 | |
| Latter (03:00-12:00)[b] | CL | 100 | (53,124) | 0.9 | (0.7,1.2) | 8.1 | (6.5,11.0) |
| | CSII | 80 | (54,113) | 0.9 | (0.6,1.2) | 8.0 | (5.2,10.4) |
| | P-value | 0.091 | | 0.056 | | 0.062 | |
| Morning (08:00-12:00)[b] | CL | 84 | (55,113) | 0.7 | (0.6,1.4) | 2.8 | (2.5,5.7) |
| | CSII | 81 | (47,100) | 0.8 | (0.6,1.2) | 3.2 | (2.5,4.7) |
| | P-value | 0.424 | | 0.398 | | 0.350 | |
| Postprandial (21:00-00.00)[a] | CL | 276 | (245,417) | 0.5 | (0.4,1.0) | 1.3 | (1.2,3.1) |
| | CSII | 337 | (261,444) | 0.9 | (0.6,1.1) | 2.7 | (1.8,3.3) |
| | P-value | 0.099 | | 0.155 | | 0.136 | |

**Notes:** * Denotes statistical significance at the 5% level. [a] calculations based on 12 subjects; [b] calculations based on 11 subjects.

the meal on 19 out of 24 study visits. On three visits, the bolus was delayed until after the meal was finished because of preceding symptomatic hypoglycaemia, as per subjects' standard practice. Figure 3.5 shows a wider interquartile range of plasma insulin concentration between approximately 21:00 and 23:00. This higher variability is likely related to the insulin bolus administered with the evening meal (Table 3.8).

Between 21:00 and midnight (postprandial period), there was a trend towards lower average insulin infusion (0.5 U/h versus 0.9 U/h; $p = 0.155$) and total insulin (1.3U versus 2.7U; $p = 0.136$) infused during closed-loop compared with CSII (Table 3.7). The lower rate of insulin infused during closed-loop between 22:00 and 00:00 is seen in Figure 3.4, and is related to the algorithm minimising insulin delivery

Figure 3.4: Insulin infusion rates during closed-loop and CSII

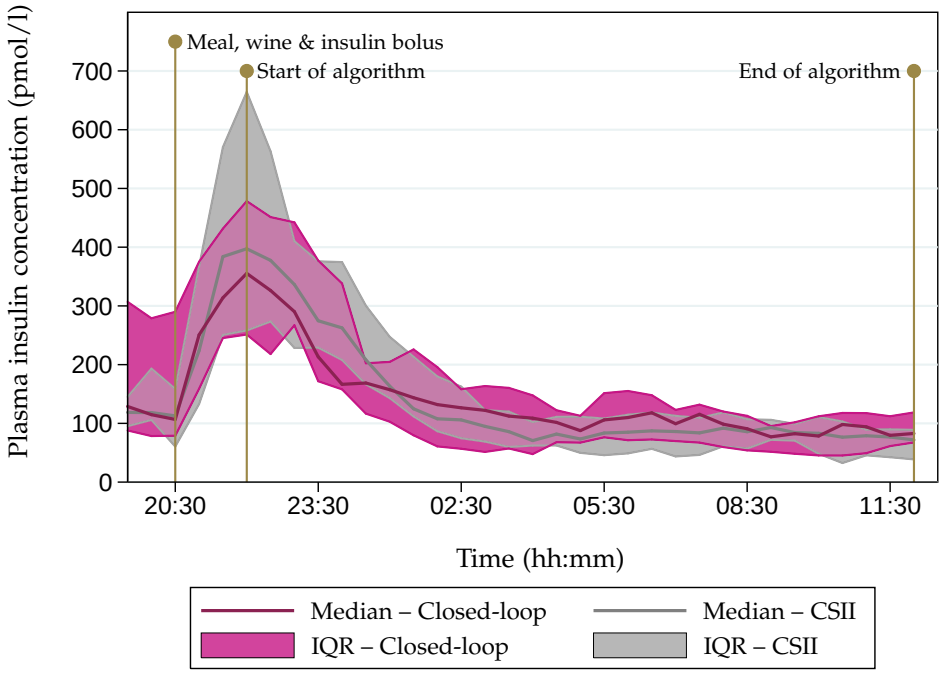



following the prandial bolus to avoid postprandial hypoglycaemia. Hence, the two episodes of hypoglycaemia that occurred during closed-loop within three hours of the meal, were most likely related to the prandial bolus.

#### 3.5.2.6 Alcohol

The average volume of wine consumed, which was matched on both study visits, was $564 \pm 133$ml. This was substantiated by the similar measured area under the ethanol concentration curve (Table 3.9). Mean peak ethanol concentration was also similar between visits (15.4 mmol/l versus 16.7 mmol/l; $p = 0.239$), and was reached approximately two hours after commencement of alcohol consumption. This compares with a maximum legal limit of 17 mmol/l for driving in the UK. Plasma ethanol levels were largely undetectable by 06:00.

Figure 3.5: Plasma insulin concentration profiles during closed-loop and CSII




Intersubject variability as assessed by the coefficient of variation was 20% for plasma ethanol and 26% for area under the ethanol concentration curve. Corresponding intrasubject variability was 21% and 19%, respectively.

On the conventional CSII visits, participants were allowed to adjust their basal rates or prandial boluses according to their routine practice when consuming alcohol. Three subjects set a temporary basal rate following the meal, ranging from a 20% to 30% reduction, between 4.5 and 10 hours in duration. The other nine subjects remained on their usual CSII regimen overnight.

#### 3.5.2.7 Morning period

The most striking improvement under closed-loop insulin delivery was seen between 08:00 and 12:00 when time spent in target was 100% during closed-loop and 40% during CSII ($p = 0.008$), and time in hyperglycaemia 0% and 41% ($p = 0.012$), respectively (Table 3.2).

Table 3.8: Carbohydrates consumed and insulin bolus administered with evening meal for each subject

| Subject | Carbohydrates (g) | Closed-loop | | CSII | |
|---|---|---|---|---|---|
| | | Insulin (U) | Time of bolus (hh:mm) | Insulin (U) | Time of bolus (hh:mm) |
| 1 | 118 | 12.5 | 20:31 | 12.5 | 20:33 |
| 2 | 107 | 14.0 | 20:33 | 14.2 | 20:36 |
| 3 | 118 | 12.2 | 20:49 | 11.5 | 20:39 |
| 4 | 116 | 7.5[a] | 21:01 | 10.0[b] | 20:47 |
| 5 | 100 | 7.5 | 20:45 | 8.5 | 20:32 |
| 6 | 100 | 24.0 | 20:47 | 24.0 | 20:31 |
| 7 | 100 | 7.0 | 20:55 | 10.0 | 21:16 |
| 8 | 100 | 9.0 | 20:34 | 10.0 | 20:34 |
| 9 | 100 | 8.3 | 20:54 | 8.3 | 20:32 |
| 10 | 100 | 6.0 | 20:58 | 8.0 | 20:33 |
| 11 | 100 | 9.0[c] | 20:31 | 8.5[d] | 20:37 |
| 12 | 100 | 14.9 | 20:30 | 14.4 | 21:04 |
| Mean | 105 | 11.0 | | 11.7 | |
| Standard deviation | 8 | 5.0 | | 4.5 | |

**Notes:** [a] 4.5U at 21:01and 3.0U over 30 minutes (dual wave); [b] 6.0U at 20:47 and 4.0U over 30 minutes (dual wave); [c] 4.5U at 20:31and 4.5U over 30 minutes (dual wave); [d] 4.25U at 20:37 and 4.25U over 60 minutes (dual wave).

Table 3.9: Summary of plasma ethanol during closed-loop and CSII

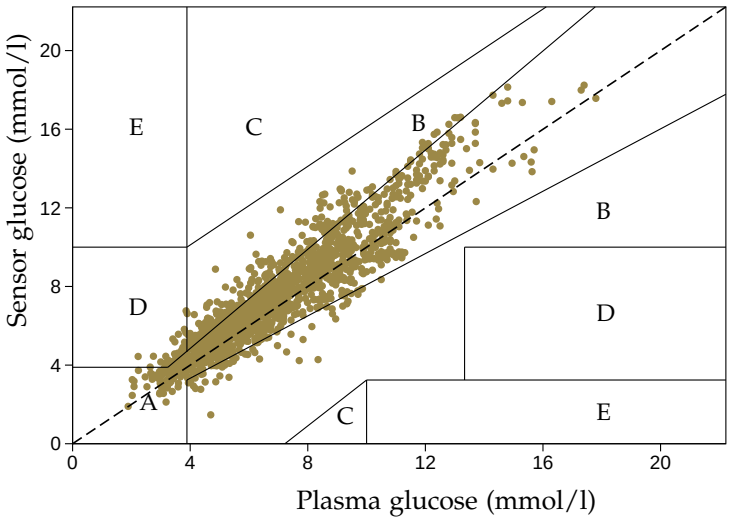
| Meal | CL | CSII | P-value |
|---|---|---|---|
| Peak concentration (mmol/l) | 15.4 $\pm$ 2.6 | 16.7 $\pm$ 3.7 | 0.239 |
| Time to peak (min) | 141 $\pm$ 64 | 110 $\pm$ 47 | 0.102 |
| AUC ethanol (mmol/l/min) | 4226 $\pm$ 1045 | 4386 $\pm$ 1203 | 0.814 |

**Notes:** Data are mean $\pm$ standard deviation. AUC denotes area under the ethanol concentration curve.

### 3.5.3 Sensor accuracy

Accuracy of the FreeStyle Navigator (Abbott Diabetes Care, Alameda, CA, USA), evaluated as median relative absolute deviation of sensor from plasma (reference) glucose values, was 12.0% (6.8%, 17.2%). This is higher than the value of 8.0% measured in the feasibility study, which may be related to the effect of the larger meal

Figure 3.6: Clarke error grid analysis showing accuracy of FreeStyle Navigator CGM




**Notes:** Values in zone A or B are clinically acceptable. Values in zone C, D or E are potentially unsafe.

and alcohol on glucose variability. The Clarke error grid analysis illustrates sensor accuracy, showing the majority of values were in zones A and B (Figure 3.6).

## 3.6 Discussion

This study evaluated overnight closed-loop insulin delivery in 12 new adults with type 1 diabetes, extending the results obtained in the earlier 'Feasibility' study detailed in Chapter 2. Closed-loop performance was tested following a larger meal (100g carbohydrate) compared with the 60g-carbohydrate meal in the feasibility study. Additionally, a moderate amount of alcohol (564ml white wine on average) accompanied the meal, similar to an evening out. Closed-loop increased the time spent in target plasma glucose ($3.9 - 8.0$ mmol/l) by 24%, identical to the improvement observed during the 'Feasibility' study, indicating that closed-loop performance was not compromised by the higher carbohydrate load and alcohol. Although glucose was in target for only 70% of time, compared with 81% during the 'Feasibility' study, corresponding time in target during conventional CSII visits was also lower (41%

versus 57%). The observed differences were likely related to the effect of consuming a larger meal and alcohol on glycaemic control, rather than the subjects studied as HbA1c was 7.8% in both cohorts at baseline. Additionally, the later commencement of closed-loop (22:00) compared with 19:00 during the 'Feasibility' study may have contributed to the lower time in target achieved, as closed-loop performance increases with longer duration of use.

During both interventions, most subjects had their prandial insulin bolus at the time of the evening meal. This may have contributed to the postprandial hyperglycaemia observed (Figure 3.3). Administration of insulin boluses 15 to 20 minutes prior to eating is associated with improved glucose control after meals.[150; 151] Overall glucose variability and time spent in hyperglycaemia were significantly lower during closed-loop, even with consumption of a high carbohydrate meal. This is noteworthy as both postprandial hyperglycaemia and glucose variability are associated with an increased risk of adverse diabetes related outcomes.[48] Compared with the 'Feasibility' study, overall glucose variability was higher, likely related to the larger meal and alcohol consumed. There was a trend towards less time spent in hypoglycaemia during closed-loop visits. There were two episodes of hypoglycaemia: both occurred before midnight, within two hours from commencement of the algorithm, and were attributed to the insulin bolus administered for the evening meal.

The degree of hypoglycaemia during conventional therapy visits was lower than expected. The occurrence of nocturnal or early morning hypoglycaemia following an evening of drinking alcohol may be especially hazardous, due to the blunting effect of alcohol on cognition in addition to a reduced arousal state during sleep. The study was designed to simulate a night out drinking alcohol followed by sleeping through until lunchtime, an occurrence that is not uncommon especially amongst younger adults. Despite achieving similar peak plasma ethanol concentrations (15.4 mmol/l during closed-loop and 16.7 mmol/l during CSII) to a previous study, in which consumption of a similar quantity of alcohol resulted in symptomatic hypoglycaemia with peak ethanol levels of 19.1 mmol/l,[158] the degree of hypoglycaemia observed during my study was lower than anticipated. One reason may have been not having breakfast and the accompanying prandial insulin bolus. Additionally, consuming alcohol concurrently with food may have reduced the bioavailability of ethanol,[162] compared with the study by Turner et al where there was a three hour interval between the evening meal and wine consumption.[158] Another explanation for the decreased rate of hypoglycaemia is that the baseline risk may have been lower in the cohort of patients evaluated in my study as they had reasonable glycaemic control

prior to study entry.

Inter- and intra-subject variability in plasma ethanol concentration as measured by the coefficient of variation was 20% and 21%, respectively. Respective values for ethanol AUC were 26% and 19%. These values are lower than previously reported in healthy young males, where inter- and intra-individual coefficient of variation for plasma ethanol were 34% and 38% respectively, with values of 44% and 35% for ethanol AUC.[162] The aetiology of the lower variability measured in my study is uncertain, as the study was not designed to evaluate such effects of ethanol ingestion. Possible contributing factors include age, quantity and strength of the alcohol consumed, and concurrent ingestion of food.[161] It is also possible that co-existing diabetes has an influence on ethanol metabolism, although this has not been previously investigated.

Continuation of closed-loop insulin delivery during the morning from 08:00 until midday resulted in an even greater benefit on glycaemic control with 100% of time spent in target glucose, compared with only 40% during conventional therapy. As drinking alcohol in the evening is associated with an increased risk of delayed hypoglycaemia, the results of my study demonstrate the potential for closed-loop to minimise hypoglycaemia whilst still achieving target glycaemic levels.

During closed-loop visits there were no plasma glucose measurements above 8.0 mmol/l after 08:00. Although breakfast with subsequent postprandial rise in glucose levels was omitted, on CSII visits over 40% of time was spent hyperglycaemic during the morning. As no prandial insulin bolus was delivered in the morning, the hyperglycaemia is likely attributed to inadequate amount of basal infusion. Insulin requirements are generally higher in the morning, associated with the dawn phenomenon.[142] Interestingly, three participants chose to set a $20-30\%$ reduction in their usual CSII rates for up to ten hours following consumption of the wine as per their usual practice. My study suggests that such reduction may not be necessary, and in fact may contribute to elevated glucose levels the following morning. However, the effect of alcohol on glycaemic control is multifactorial, hence the results of this study cannot be applied to all patients with type 1 diabetes and to all situations involving alcohol consumption.

One of the major strengths of this study was evaluating a common scenario which can be challenging for people with type 1 diabetes, in particular the increased risk of delayed hypoglycaemia after drinking alcohol. The size and timing of the meal and wine were chosen to replicate real life as closely as possible. This enabled in-clinic evaluation of closed-loop following a common situation prior to outpatient testing.

This study provided an insight into self-management routines in insulin therapy in a small cohort of patients with type 1 diabetes. During conventional CSII visits subjects were advised to make adjustments to their insulin regimen as they would usually do at home when drinking alcohol. Only three subjects adjusted their usual insulin regimen for alcohol. The majority reported that they would normally consume a snack before bedtime to prevent late hypoglycaemia, which they found to be less complicated than adjusting basal rates or prandial insulin boluses. Subjects administered insulin for the evening meal according to their standard practice, with only two choosing an extended bolus despite the larger meal consumed.

The reasonably well-controlled cohort of subjects studied may have limited evaluation of the true hypoglycaemic effect of alcohol in patients with type 1 diabetes. The response to alcohol consumption seen in the cohort of patients studied may not be comparable to the effect of drinking in all people with type 1 diabetes. Similarly, consumption of other types of alcohol such as beer or not eating whilst drinking are likely to have a different effect on glucose levels.

## 3.7 Conclusion

This is the second randomised overnight closed-loop study in adults with type 1 diabetes, extending the results of the 'Feasibility' study. Closed-loop performance was not compromised by consuming a large carbohydrate meal and drinking alcohol. Compared with conventional insulin pump therapy, closed-loop increased time spent with plasma glucose in target range, lowered time spent in hyperglycaemia and reduced glucose variability. Closed-loop insulin delivery was safe, with no episodes of hypoglycaemia after midnight.

# Chapter 4

# Daytime closed-loop insulin delivery during pregnancy

## 4.1 Background

### 4.1.1 Physiology of pregnancy

Pregnancy is regarded as a diabetogenic state with increasing insulin resistance as gestation progresses, attributed to increased production of insulin antagonising hormones including cortisol, progesterone, oestrogen, prolactin and leptin. In response to increasing foetal demands, gluconeogenesis also increases with advancing pregnancy.[165]

### 4.1.2 Glycaemic control and obstetric outcomes

Less than a third of women with diabetes receive adequate preconception care.[166] A population study from the Netherlands reported a significantly lower risk of congenital anomalies in planned (4%) versus unplanned (12%) pregnancies.[167] A UK cohort study of 290 women with type 1 diabetes found a strong association between prepregnancy care and improved early glycaemic control, with resulting lower foetal malformation and premature delivery rates.[168]

Suboptimal glycaemic control in diabetic pregnancy is linked with significantly increased rates of adverse obstetric and neonatal outcomes.[167; 169; 170] As the transfer of nutrients across the placenta is concentration dependent, maternal hyperglycaemia will have a direct effect on the foetus.[171] In addition, as free insulin cannot cross the placenta, metabolism of maternal nutrients is dependent on foetal

insulin secretion. Episodic rises in maternal glucose levels, during the second and third trimesters, may stimulate foetal hyperinsulinism which promotes development of macrosomic or large for gestational age infants.[172; 173] Macrosomia is common, occurring in approximately 50% of women with diabetes, and is associated with delivery-related complications as well as an increased risk of insulin resistance, obesity and diabetes in offspring later in life.[174]

The largest reported population-based study, carried out in Sweden, showed considerably higher rates of preeclampsia (odds ratio 4.5), preterm delivery (odds ratio 4.9), stillbirth (odds ratio 3.34), perinatal mortality (odds ratio 3.3), major congenital malformations (odds ratio 2.5) and macrosomia (odds ratio 11.5) in women with type 1 diabetes compared with healthy controls.[169] The 2006 Confidential Enquiry into Maternal and Child Health in the UK reported a four times greater risk of perinatal mortality and two times greater risk of congenital malformations in pregnant women with type 1 or 2 diabetes compared with healthy controls.[170]

During the DCCT trial, there were 270 pregnancies in 180 women.[175] Mean HbA1c was 7.4% in the intensive group and 8.1% in the conventional therapy group at conception, but similar during gestation (HbA1c 6.6%). Of the 86 women in the conventional group, there was no difference in adverse outcomes between those who switched to intensive therapy before versus after conception. There were nine (4.7%) congenital malformations overall: eight occurred in women originally in the conventional group, three of which were considered unrelated to diabetes.

### 4.1.3 Hypoglycaemia

Pregnancy is associated with an increased risk of hypoglycaemia, particularly in early gestation when the risk of severe hypoglycaemia is increased three to five fold compared with prepregnancy rates.[176] One third of women with no prior history of severe hypoglycaemia may experience an episode during pregnancy. Intensification of insulin therapy to minimise hyperglycaemia is commonly implicated.[177] However, post hoc analysis of the DCCT suggested that intensive insulin therapy was not associated with hypoglycaemia during pregnancy.[175] During early pregnancy, contributing factors include a reduction in hypoglycaemia awareness, pregnancy induced nausea and vomiting, and a relatively lower insulin requirement.[176] An observational study in Denmark found a severe hypoglycaemia rate of 5.3, 2.4 and 0.5 events per patient years in trimesters 1, 2 and 3, respectively, with 45% of women experiencing at least one event during pregnancy.[177] Both severe hypoglycaemia

pre-conception and reduced hypoglycaemia awareness were independent predictors of severe hypoglycaemic events. Other risk factors include longer duration of diabetes and tight glycaemic control (HbA1c $< 6.5\%$).[176; 177]

Recurrent hypoglycaemia and diabetes progression result in impaired glucose counter-regulation and the associated phenomenon of hypoglycaemia unawareness, both of which may be exacerbated during pregnancy. Clamp studies in women with type 1 diabetes during pregnancy demonstrated significantly diminished epinephrine and growth hormone responses to hypoglycaemia, compared with the non-pregnant state. In healthy controls, the normal glucagon response to hypoglycaemia was diminished during pregnancy.[178]

Severe hypoglycaemia is the leading cause of maternal death in type 1 diabetes. A case review from Finland reported five deaths amongst 972 pregnant women with type 1 diabetes (0.5%), two of which were attributed to hypoglycaemia.[179] A cohort study of 323 pregnant women with type 1 diabetes from the Netherlands reported two deaths (0.6%), one of which was due to severe hypoglycaemia.[167] These figures represent a 60-fold increased mortality rate in women with type 1 diabetes compared with the normal population.

The effect of maternal hypoglycaemia on offspring is less well understood. A teratogenic effect of even brief periods of hypoglycaemia resulting in developmental anomalies and growth retardation has been seen in animal studies.[180; 181] Such outcomes have not been observed in humans, although no studies have specifically evaluated the vulnerable period of embryogenesis in early gestation, when the embryo is wholly dependent on maternal glycolysis.[182] As transplacental glucose transport is dependent on the maternal-foetal concentration gradient, a reduction in maternal glucose levels may compromise foetal nutrition, resulting in an increased risk of intrauterine growth restriction. Small for gestational age infants have been observed to have higher rates of adverse neonatal outcomes.[183] Neonatal, but not maternal, hypoglycaemia has been shown to be associated with neurological deficits in the long term.[184]

### 4.1.4 Challenges to daytime glycaemic control

Aiming for near-normoglycaemia, including minimising fluctuations in glucose levels, is imperative to achieving favourable obstetric outcomes. During the daytime, glucose control may be influenced by meals (as detailed in Chapter 3) and physical activity.

#### 4.1.4.1 Glycaemic effects of exercise

Physical activity, in contrast to the effect of a meal or insulin bolus, has longer lasting and more dynamic consequences on glucose-insulin regulation in type 1 diabetes. The magnitude of effect depends on multiple factors including insulin therapy, prior carbohydrate consumption, exercise duration and intensity, cardiovascular fitness and pre-exercise glucose levels. The major factors influencing glucose uptake into muscle during exercise include insulin-independent translocation of glucose transporter proteins (primarily glucose transporter 4) from an intracellular store to the plasma membrane, blood glucose concentration, capillary blood flow, and glucose phosphorylation. In comparison with the sedentary state, where glucose transport is the major rate-limiting step, phosphorylation has a greater influence during exercise.[185]

In healthy individuals, exercise stimulates suppression of insulin secretion with resulting increased hepatic glucose production, lipolysis and reduced peripheral glucose uptake. In type 1 diabetes, elevated therapeutic insulin levels inhibit hepatic glucose production which is required to meet the glucose demand by exercising muscles, leading to an increased risk of hypoglycaemia. Activation of counter-regulatory hormones, which normally contribute to restoration of glucose levels and triggering of neuroglycopaenic symptoms during exercise, are reduced or absent.[186] The behavioural response is hence compromised with resulting failure to recognise symptoms and initiate rescue carbohydrate treatment. The beneficial effect of exercise itself on peripheral insulin sensitivity also contributes to hypoglycaemia. The risk of hypoglycaemia is even greater during pregnancy due to increased energy demands placed by the foetus as well as the tighter glycaemic targets necessitated to avoid hyperglycaemia-related adverse obstetric outcomes.

#### 4.1.4.2 Exercise intensity

Low to moderate intensity exercise is associated with a greater risk of hypoglycaemia.[187] More intense activity induces a rise in catecholamines, cortisol and growth hormone, resulting in hyperglycaemia.[188] During recovery in healthy individuals, catecholamine levels decrease and insulin secretion is increased, resulting in normalisation of glucose. In type 1 diabetes, the absence of a rise in endogenous insulin secretion during recovery results in prolonged hyperglycaemia. The hyperinsulinaemia may be mimicked with administration of a correction bolus,[189] but a subsequent snack may be required to prevent later hypoglycaemia. Intermittent

high intensity exercise, compared with moderate intensity exercise alone, is associated with a lower rate of hypoglycaemia.[190] Inclusion of a ten second sprint has been shown to limit the risk of post-exercise hypoglycaemia.[191]

#### 4.1.4.3 Exercise timing

The scheduling of exercise in relation to timing of meals, insulin and other activity has a significant influence on glycaemic outcomes. The risk of hypoglycaemia is lower when exercise is carried out several hours after a meal, known as the post-absorptive state.[192] Exercising prior to administration of insulin for breakfast may provide added protection as circulating insulin levels are low, and liver and muscle glycogen stores are replete. Compared with afternoon exercise, pre-breakfast exercise in six subjects with type 1 diabetes was associated with higher glucose and cortisol levels with a subsequent lower risk of hypoglycaemia.[193]

The glucose-lowering effects of exercise may persist for several hours, associated with increased tissue insulin sensitivity and physiological repletion of depleted muscle glycogen stores. Late afternoon exercise is associated with an increased risk of nocturnal hypoglycaemia, as indicated by a biphasic increase in glucose utilisation at the end of exercise and again $7-11$ hours later in adolescents with type 1 diabetes.[194] Late afternoon exercise in 50 youth with type 1 diabetes resulted in lower mean overnight glucose of 7.3 mmol/l versus 8.6 mmol/l when no exercise was performed.[195] Pre-exercise and pre-bedtime snack glucose levels were the strongest predictors of hypoglycaemia risk.

#### 4.1.4.4 Preceding exercise or hypoglycaemia

Repeated episodes of hypoglycaemia result in progressive blunting of the counter-regulatory response causing a vicious cycle of recurrent hypoglycaemia, termed hypoglycaemia associated autonomic failure.[186] Glucagon, epinephrine and cortisol responses were markedly reduced during exercise the day after two episodes of hypoglycaemia in 16 adults with type 1 diabetes.[196] A three-fold increased glucose infusion rate was required to maintain euglycaemia. Post hoc analysis of the DCCT cohort found that unusual physical activity was more frequent on days when severe hypoglycaemia occurred although this association was not significant.[119] Prior exercise has also been shown to reduce the counter-regulatory response to subsequent exercise with ensuing increased risk of hypoglycaemia.[197]

#### 4.1.4.5 Managing glucose levels during exercise

Conventional strategies to avoid hypoglycaemia include adjusting insulin doses and/or consuming additional carbohydrates before and after exercise. One recommendation is consuming 15g carbohydrate prior and every $30-60$ minutes during exercise, with larger quantities for more intense activity.[192] Excess carbohydrate supplementation may lead to hyperglycaemia. Consumption of low glycaemic index compared with high glycaemic index foods may provide more stable glucose levels.[198]

Reduction in insulin taken for meals, proportionate to exercise intensity and duration, may lower the risk of hypoglycaemia.[199] Temporary suspension of basal insulin pump therapy for exercise has been shown to reduce hypoglycaemia in children with type 1 diabetes.[200; 201] The main risk is hyperglycaemia and ketoacidosis, which may be further exacerbated by the metabolic changes associated with exercise.[202] Reduction in pre-exercise prandial insulin of up to 75% did not result in increased ketone body formation.[203] Discontinuation of CSII for three hours during exercise resulted in an elevated but safe level of ketone body formation, compared with no exercise.[204]

Insulin absorption from subcutaneous tissue may be increased during exercise. Postulated mechanisms include increased local blood flow and/or mobilisation from the subcutaneous depot due to a pumping effect of contracting muscles. Evidence from studies conducted almost 30 years ago, demonstrated increased insulin concentrations with injection of insulin into exercising limbs.[205; 206] However, the older insulin formulations and measurement methods employed in these studies limit applicability in current practice. There is minimal evidence regarding absorption of insulin from CSII catheter site during exercise. Plasma insulin levels were observed to increase at the end of 20 minutes of running on a treadmill, with a decrease to baseline within 10 minutes in 12 CSII-treated adults.[207]

### 4.1.5 Glucose monitoring

Frequent monitoring of glucose is essential to maintaining tight glycaemic control during pregnancy. HbA1c is usually measured at booking, $16-20$ weeks and 28 weeks gestation. UK National Institute for Health and Clinical Excellence guidelines recommend a preconception HbA1c as close to 6.1% as can be safely achieved without increasing the risk of hypoglycaemia.[94] The DCCT showed a dose-dependent relationship between HbA1c and adverse outcomes.[175] In another study, congenital malformation and perinatal mortality rates were increased four and seven-fold,

respectively, at HbA1c levels above 10.4%.[208] However, interpretation of HbA1c is limited during pregnancy due to the dynamic changes that occur to red blood cells, including increased cell turnover and erythropoietin levels, and the effects of haemodilution with increasing gestation.[209] The 2005 Confidential Enquiry into Maternal and Child Health report noted that 25% of women whose offspring had an anomaly had achieved an HbA1c below 7% by 13 weeks gestation, suggesting that 'near optimal' glycaemic control at the end of the first trimester is already too late for prevention of congenital anomalies.[210]

The emergence of CGM over the last decade has revolutionised the monitoring of diabetes. Its use in pregnancy is especially valuable in detecting the dynamic glucose excursions not apparent with conventional fingerprick glucose tests or HbA1c monitoring.

### 4.1.6 Treatment

Insulin needs in diabetic pregnancy vary considerably, associated with increasing insulin resistance as gestation progresses. In a study of 65 women with well controlled type 1 diabetes, insulin doses ranged from $0.6 - 1.1$ U/kg/day with a peak in week nine, nadir in week 16, and greater peak in week 37.[211] The majority of women are treated by multiple daily injection therapy. Insulin pumps or CSII may provide more flexibility during pregnancy, when changing eating patterns, morning sickness, reduced exercise capacity and a growing foetus may variably affect glucose levels.[212] Currently, CSII is only recommended for women inadequately controlled on multiple daily injections or with severe hypoglycaemia. Both a meta-analysis [213] and a Cochrane review [214] from 2007 found no difference in pregnancy outcomes and glycaemic control between CSII and multiple daily injection therapy. The majority of studies were observational with small numbers and evaluated the older soluble insulins.

## 4.2 Rationale

Despite the recent availability of continuous glucose monitoring and ongoing refinement of insulin replacement regimens, many women still fail to meet glucose targets during pregnancy.[215] Optimal treatment of diabetes during pregnancy necessitates avoidance of both hyperglycaemia and hypoglycaemia whilst maintaining glucose levels within a narrow range. As a result of the changing insulin requirements during

pregnancy, frequent antenatal review and fine tuning of insulin regimens is essential in order to optimise glucose control. This requires considerable allocation of time and health care resources as well as patient motivation and co-operation.

A closed-loop system, which employs a computerised control algorithm to link insulin delivery with CGM in real-time, may provide improved glycaemic control. A feasibility study carried out in ten pregnant women with type 1 diabetes confirmed safety of closed-loop insulin delivery with no hypoglycaemia events overnight.[108] Postprandial control was more challenging, with $28-44\%$ of time spent hyperglycaemic after breakfast. Daytime glucose control requires consideration of carbohydrates consumed and physical activity performed. The feasibility study in pregnancy was carried out during sedentary conditions, and hence did not include typical 'real life' activities such as housework or exercise. Before proceeding to studies in the home setting, it is essential to evaluate the closed-loop system during normal daytime activities.

## 4.3 Aim

To evaluate the efficacy of closed-loop insulin delivery to maintain glucose levels within target range ($3.5-7.8$ mmol/l), compared with conventional insulin pump therapy, during normal daily activities in pregnant women with type 1 diabetes.

## 4.4 Methods

### 4.4.1 Participants

Between April 2010 and April 2011, 12 women with type 1 diabetes were recruited from antenatal diabetes outpatient clinics at Addenbrooke's Hospital, Cambridge, and King's Hospital, London. Inclusion criteria were age 16 to 44 years, type 1 diabetes (World Health Organisation criteria [2]) for at least 12 months, current insulin pump therapy, and a viable singleton pregnancy confirmed by ultrasound. Subjects were excluded if they had non-type 1 diabetes, any major conditions or concurrent medications likely to interfere with interpretation of the study results, any clinically significant diabetes-related complications or severe hypoglycaemia, poorly controlled diabetes (HbA1c $\geq$ 10%), significant obesity (BMI $>$ 35 kg/m$^2$), insulin resistance defined by total daily dose $\geq$ 1.5 U/kg at booking, or had conceived via *in vitro* fertilisation or assisted reproductive techniques.

### 4.4.2 Study design

The study had an open randomised crossover design. The protocol was approved by the Cambridge Research Ethics Committee, and carried out in accordance with the Declaration of Helsinki. Once written informed consent was obtained, participants were randomised to attend the Wellcome Trust clinical research facility, Cambridge for two 24-hour visits (closed-loop and control), one to six weeks apart. The study protocol, which was matched on both visits, was designed to mimic a typical day at home or work (Figure 4.1).

A continuous glucose sensor was inserted at least 24 hours prior to study visits. Women were given basic training and instructions on insertion, calibrations and alarms. On arrival for the study visit at midday, an intravenous cannula was inserted for blood sampling of glucose and insulin. Following a standardised light lunch, a lightweight (10g) combined heart rate and accelerometer device (Actiheart, Cam Ntech Ltd, Papworth, UK) was attached (Figure 4.2). The Actiheart was individually calibrated at each study visit with a ramped step test which involved eight minutes of stepping at progressively increasing frequency followed by two minutes of recovery.[216]

The subject's insulin pump was disconnected and the study pump (Animas 2020 Johnson & Johnson, New Jersey, USA), delivering rapid acting insulin analogue aspart (Novo Nordisk, Bagsvaerd, Denmark), connected to the established subcutaneous insulin infusion site. On the closed-loop visit, insulin was delivered based on the advice of a model predictive control algorithm tested in the previous feasibility study in pregnancy,[108] from 14:00 until 12:30 the next day. The closed-loop system was used in the manual mode. Versions 0.03.03 to 0.03.11 of the algorithm, which is described in detail in Section 2.4.2, were used in the study. During closed-loop, meals, moderate intensity exercise and hypoglycaemia requiring treatment with rescue carbohydrates were announced to the algorithm. Snacks were not announced unless an accompanying insulin bolus was administered.

On the control visit, subjects continued their usual insulin pump regimen via the study pump. Women did not have access to CGM and any adjustments, such as setting a temporary basal rate for exercise or reducing the pre-exercise meal insulin bolus, were made using fingerprick glucose measurements.

The study visit concluded at 12:30, with subjects consuming a lunch meal of their choice prior to discharge home.

Figure 4.1: Timeline of study procedures




**Notes:** Closed-loop and control (CSII) interventions were carried out in random order, with a one to six week interval between visits.

Figure 4.2: Actiheart monitor


#### 4.4.2.1 Normal daily activities and exercise

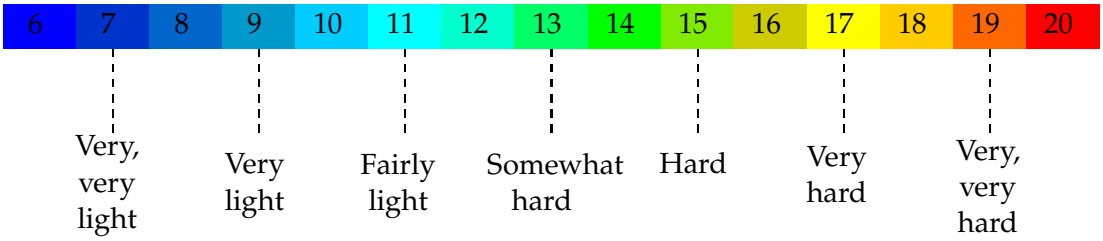
The physical activity was designed to match average levels of physical activity energy expenditure (PAEE) in pregnancy based on previous literature.[217; 218; 219] Normal daily activities included three 20-minute low intensity walks within the hospital one to two hours after meals (14:00, 19:30 and 09:00) at the participants' own speed. There were two scheduled 55-minute sessions of moderate intensity exercise, at 15:00 and 09:30. Each session involved two 25-minute periods of brisk walking on a treadmill with a five-minute rest interval. The afternoon exercise incorporated 25 minutes of walking at 4.8 km/hour with no gradient followed by 25 minutes at 2.6 km/hour at 10% incline. The morning exercise involved two 25-minute sessions of walking at 3.9 km/hour with no gradient.

The Borg rating of perceived exertion, shown in Figure 4.3 was used every 10 minutes during exercise to assess womens' effort level.[220] The scale, which correlates with increasing exercise intensity for work on a cycle ergometer, ranges from $6-20$ corresponding to heart rate ranging from $60-200$ beats per minute. In between the scheduled walks and exercise sessions, women undertook sedentary tasks such as working on a computer or watching television and went to sleep according to their preference.

#### 4.4.2.2 Meals and snacks

Participants were given pre-selected standardised meals (50g carbohydrate lunch, 60g carbohydrate evening meal, 50g carbohydrate breakfast) and a 15g carbohydrate snack before bed. Lunch consisted of a ham, tuna or cheese salad sandwich and a 15g carbohydrate snack. Evening meal options included chicken with mashed potato, beef lasagne with garlic bread or pasta. Wholegrain toast with jam or fruit, or whole-

Figure 4.3: The Borg rating of perceived exertion scale




grain breakfast cereal and fruit with milk were consumed for breakfast. Snack choices included yoghurt, fruit, crisps, biscuits and chocolate.

Prior to each meal, subjects performed a capillary fingerprick glucose test and calculated the prandial bolus to be administered using their own pump bolus wizard or insulin to carbohydrate ratios. The bolus was administered ten minutes prior to eating, unless fingerprick glucose was below 4.0 mmol/l in which case it was given with the meal. Insulin was taken for snacks according to subjects' discretion based on results of fingerprick glucose testing alone.

Exercise snacks were consumed according to fingerprick capillary glucose measured 30 minutes prior to exercise: 15g carbohydrate snack for glucose $>$ 6 mmol/l, and 30g carbohydrate snack for glucose $\leq$ 6 mmol/l. The study protocol was amended to include extra snacks after each 25-minute treadmill session for glucose $\leq$ 6 mmol/l, following an interim review which showed a high frequency of hypoglycaemia associated with moderate intensity exercise in the first six participants.

#### 4.4.2.3 Hypoglycaemia

Rescue carbohydrate (15g) as 90ml Lucozade Energy drink (GlaxoSmithKline, UK) was given to treat episodes of hypoglycaemia, defined as plasma glucose $\leq$ 3.0 mmol/l with symptoms or $\leq$ 2.5 mmol/l without symptoms. Plasma glucose levels were repeated every 15 minutes until hypoglycaemia resolved with additional treatment if required.

#### 4.4.2.4 Randomisation and blinding

Block randomisation was used to allocate subjects to the order in which they completed their study visits. Subjects were blinded to CGM and plasma glucose values on both visits. For safety reasons, investigators had access to plasma glucose levels.

### 4.4.3 Measurements

#### 4.4.3.1 Plasma glucose and insulin

Blood sampling for glucose and insulin was carried out at 15 and 30 minute intervals from 14:00 until study end at 12:30 the following day. Whole blood samples were immediately centrifuged, and plasma aliquoted into separate tubes. Plasma glucose was measured in real-time on a YSI 2300 STAT Plus analyser (YSI, Fleet, UK). Plasma insulin was stored frozen, for later analysis by immunochemiluminometric assay (Invitron Ltd, Monmouth, UK).

#### 4.4.3.2 Continuous glucose monitor

The FreeStyle Navigator CGM (Abbott Diabetes Care, Alameda, CA, USA) with a one hour run-in calibration period was used (Figure 1.1).

#### 4.4.3.3 Physical activity energy expenditure (PAEE)

PAEE was measured using the Actiheart (Cam Ntech Ltd, Papworth, UK) device consisting of two electrodes connected by a short lead which attach to the chest surface via two electrocardiogram pads (Figure 4.2). It has been validated outside of pregnancy, with reported intra-device coefficient of variation of 0.5% and 0.03% and inter-device coefficient of variation of 5.7% and 0.03%, for movement and heart rate respectively.[221] The device was set to record at 30-second epochs.

### 4.4.4 Statistical analysis

For this exploratory safety study, the sample size was pragmatic based on a previous feasibility study of closed-loop in pregnant women with type 1 diabetes.[108]

The primary outcome was time spent with plasma glucose in the target range ($3.5 - 7.8$ mmol/l), based on National Institute for Health and Clinical Excellence guidelines for pregnancy,[94] from 14:00 on day one to 12:30 on day two.

Pre-defined secondary outcomes were time spent above ($>$ 7.8 mmol/l and $>$ 10.0 mmol/l) and below ($\leq$ 3.5 mmol/l and $\leq$ 2.8 mmol/l) target, mean glucose concentration, standard deviation of glucose, the low blood glucose index, mean insulin infusion rate and plasma insulin concentration. Secondary outcomes were calculated for both plasma and sensor glucose, for the following time periods:

- **Overall period (14:00-12:30).** The 'overall period' evaluated glycaemic control from study commencement at 14:00 until study end at 12:30 the following day.
- **Afternoon (14:00-18:00).** The 'afternoon period' evaluated glycaemic control during moderate intensity exercise from 15:00 to 16:00 and the two hour recovery period post exercise.
- **Evening (18:00-23:00).** The 'evening period' evaluated postprandial glycaemic control following the evening meal at 18:00.
- **Overnight (23:00-07:30).** The 'overnight period' evaluated fasting glycaemic control.
- **Morning (07:30-12:30).** The 'morning period' evaluated glycaemic control following breakfast at 07:30 in addition to during moderate intensity exercise from 09:30 to 10:30 and the two hour recovery period post exercise.

Statistical analyses were conducted using SPSS, Version 15 (SPSS Inc, Chicago, IL, USA) and GStat software Version 1.1.2 (University of Cambridge, UK). Activity energy expenditure was analysed using the Actiheart software programme.[222]

## 4.5 Results

Twelve women completed both study visits. Demographic data are summarised in Table 4.1. Ten women commenced CSII pre-conception, seven were primiparous, and all lived with a partner. Of the total cohort, nine were on aspart and three on lispro rapid acting insulin analogue at baseline. The average time between study visits was $27 \pm 11$ days.

### 4.5.1 Primary outcome

There was no difference in the overall time spent with plasma glucose concentration in target range for pregnancy ($3.5 - 7.8$ mmol/l) between closed-loop and conventional CSII visits; 81% versus 81%; $p = 0.754$ (Table 4.2). This is illustrated in Figure 4.4 by the very similar median glucose profiles.

Table 4.1: Demographics of 12 participants

| Characteristic | Mean | Standard deviation |
|---|---|---|
| Age (years) | 33.5 | 4.0 |
| Gestation at visit 1 (weeks) | 21.1 | 5.7 |
| Gestation at visit 2 (weeks) | 23.9 | 5.4 |
| Diabetes duration (years) | 18.0 | 9.4 |
| Pump duration (years) | 2.8 | 3.4 |
| Booking HbA1c (%) | 7.2 | 1.0 |
| Pre-study HbA1c (%) | 6.4 | 0.5 |
| Weight visit 1 (kg) | 77.3 | 9.8 |
| Body mass index visit 1 (kg/m$^2$) | 27.8 | 3.1 |
| Total daily insulin visit 1 (U) | 50.9 | 20.1 |
| Total daily insulin visit 2 (U) | 58.4 | 22.9 |

Figure 4.4: Plasma glucose profiles during closed-loop and CSII

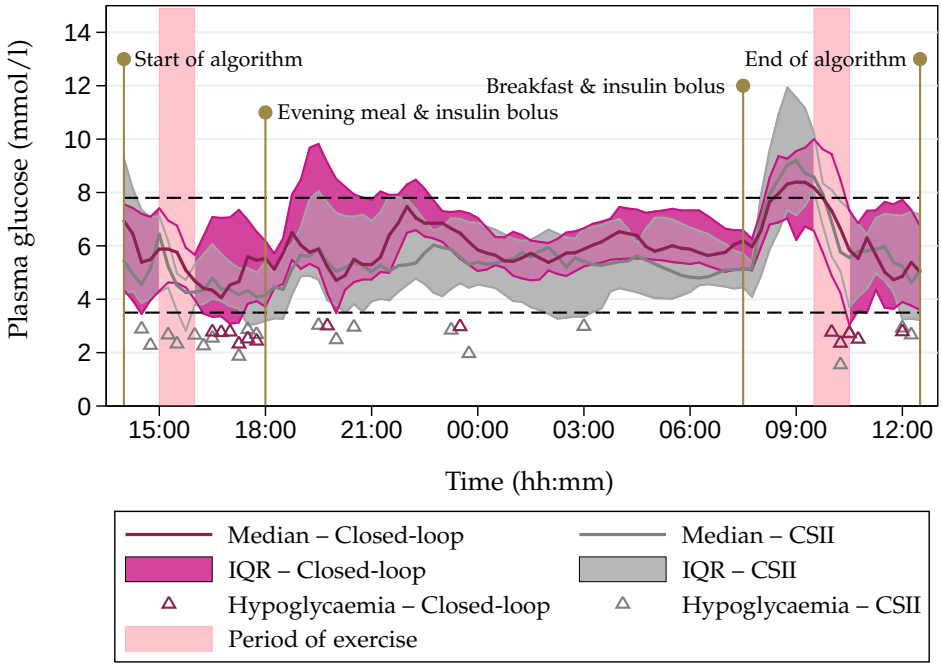
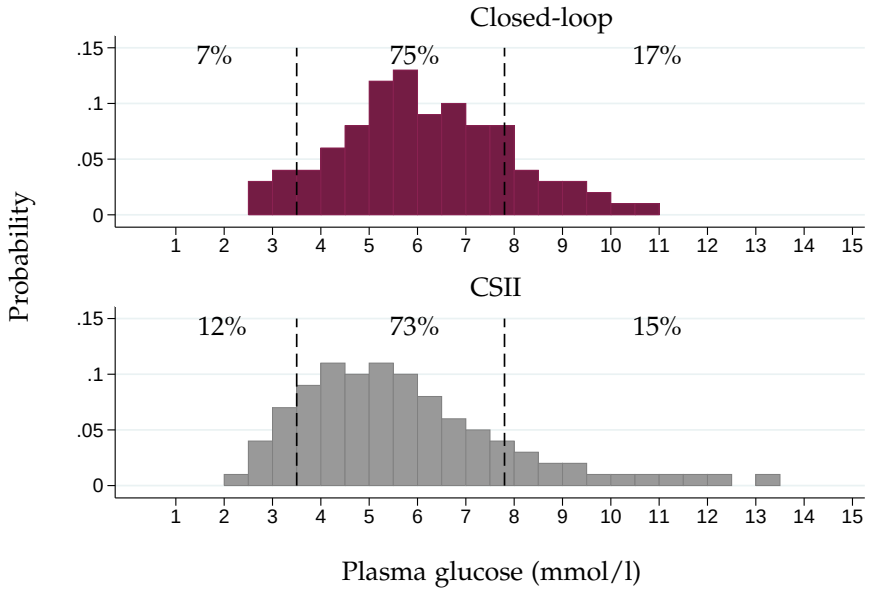


Figure 4.5: Distribution of plasma glucose during closed-loop and CSII




**Notes**: Percent values denote proportion of glucose measurements within, above and below target (3.5 – 7.8 mmol/l).

### 4.5.2 Secondary outcomes

#### 4.5.2.1 Overall glucose control

Secondary outcome data are summarised in Table 4.2. There was no difference in mean plasma glucose concentration between visits; 6.2 mmol/l versus 5.8 mmol/l, $p = 0.347$. Closed-loop lowered the time spent below 2.5 mmol/l (0.0% versus 0.3%; $p = 0.044$) and the low blood glucose index (2.4 versus 3.3; $p = 0.034$). This is displayed in Figure 4.5 by the higher proportion of values below 3.5 mmol/l during CSII. The proportion of values in hyperglycaemic range was similar between interventions, although there was a greater frequency of values at higher glucose concentrations (11 – 14 mmol/l) during CSII. Using sensor glucose measurements, secondary outcomes were similar between closed-loop and CSII visits (Table 4.3).

Individual plasma and sensor glucose profiles for each subject are provided in Appendix A.

Table 4.2: Plasma glucose and insulin outcomes during closed-loop and CSII for overall and overnight periods

| | Overall (14:00-12:30) | | | Overnight (23:00-07:30) | | |
|---|---|---|---|---|---|---|
| | CL | CSII | P-value | CL | CSII | P-value |
| *Primary Outcome (in target)* | | | | | | |
| $3.5 <$ Plasma glucose $\leq 7.8$ mmol/l (%) | 81 (59, 88) | 81 (54, 90) | 0.754 | 95 (84, 100) | 100 (64, 100) | 0.484 |
| *Secondary Outcomes* | | | | | | |
| Mean plasma glucose (mmol/l) | $6.2 \pm 0.8$ | $5.8 \pm 1.1$ | 0.347 | $6.1 \pm 0.8$ | $5.7 \pm 2.2$ | 0.272 |
| Starting plasma glucose (mmol/l) | $6.3 \pm 1.8$ | $6.4 \pm 2.6$ | 0.722 | $6.8 \pm 1.8$ | $5.6 \pm 1.4$ | 0.041* |
| Plasma glucose $\leq 3.5$ mmol/l (%) | 7 (1, 12) | 8 (4, 18) | 0.480 | 0 (0, 0) | 0 (0, 19) | 0.249 |
| Plasma glucose $\leq 2.8$ mmol/l (%) | 1 (0, 2) | 2 (0, 3) | 0.169 | 0 (0, 0) | 0 (0, 0) | 0.317 |
| Plasma glucose $< 2.5$ mmol/l (%) | 0.0 (0.0, 0.2) | 0.3 (0.0, 1.5) | 0.044* | — | — | |
| Low blood glucose index | 2.4 (0.9, 3.5) | 3.3 (1.9, 5.1) | 0.034* | 0.8 (0.2, 1.3) | 2.4 (0.3, 6.1) | 0.117 |
| Plasma glucose $> 7.8$ mmol/l (%) | 14 (7, 28) | 7 (6, 22) | 0.754 | 0 (0, 13) | 0 (0, 0) | 0.715 |
| Plasma glucose $> 10.0$ mmol/l (%) | 0 (0, 6) | 0 (0, 6) | 0.779 | 0 (0, 0) | 0 (0, 0) | 0.317 |
| Standard deviation of plasma glucose (mmol/l) | 1.4 (1.3, 2.1) | 1.6 (1.4, 2.3) | 0.695 | 0.8 (0.5, 1.0) | 0.8 (0.5, 1.0) | 0.754 |
| Insulin infusion (U/h) | 0.7 (0.5, 0.9) | 0.8 (0.5, 1.1) | 0.347 | 0.9 (0.6, 1.1) | 0.9 (0.5, 1.2) | 0.388 |
| Plasma insulin concentration (pmol/l) | 120 (101, 146) | 107 (82, 145) | 0.875 | 63 (46, 84) | 55 (37, 87) | 0.810 |

**Notes**: Data are mean $\pm$ standard deviation or median (interquartile range). *Denotes statistical significance at the 5% level.

Table 4.3: Sensor glucose outcomes during closed-loop and CSII for overall and overnight periods

| | Overall (14:00-12:30) | | | Overnight (23:00-07:30) | | |
|---|---|---|---|---|---|---|
| | CL | CSII | P-value | CL | CSII | P-value |
| $3.5 <$ Sensor glucose $\leq 7.8$ mmol/l (%) | 79.0 (69, 85) | 81.0 (57, 86) | 0.480 | 98.0 (94, 100) | 83.0 (50, 100) | 0.034* |
| Mean sensor glucose (mmol/l) | $6.3 \pm 0.5$ | $6.2 \pm 1.2$ | 0.388 | $5.8 \pm 0.4$ | $5.9 \pm 2.7$ | 0.583 |
| Starting sensor glucose (mmol/l) | $7.1 \pm 1.8$ | $7.5 \pm 2.8$ | 0.646 | $6.8 \pm 1.84$ | $5.9 \pm 1.3$ | 0.041* |
| Sensor glucose $\leq 3.5$ mmol/l (%) | 2 (1, 7) | 5 (0, 19) | 0.308 | 1 (0, 3) | 0 (0, 29) | 0.328 |
| Sensor glucose $\leq 2.8$ mmol/l (%) | 0 (0, 2) | 0 (0, 3) | 0.344 | 0 (0, 0) | 0 (0, 1) | 0.144 |
| Low blood glucose index | 1.7 (1.2, 3.1) | 2.3 (0.7, 5.1) | 0.209 | 1.3 (0.8, 2.0) | 2.3 (0.1, 8.6) | 0.239 |
| Sensor glucose $> 7.8$ mmol/l (%) | 16 (14, 25) | 17 (10, 24) | 0.814 | 1 (0, 2) | 0 (0, 3) | 0.779 |
| Sensor glucose $> 10.0$ mmol/l (%) | 2.6 (0.0, 10.0) | 3.5 (1.7, 6.4) | 0.790 | 0.0 (0.0, 0.0) | 0.0 (0.0, 0.0) | 0.317 |
| Standard deviation of sensor glucose (mmol/l) | 1.7 (1.5, 2.2) | 1.7 (1.4, 2.4) | 0.814 | 0.9 (0.8, 1.1) | 0.8 (0.6, 1.1) | 0.695 |

**Notes**: Data are mean $\pm$ standard deviation or median (interquartile range). *Denotes statistical significance at the 5% level.

#### 4.5.2.2 Overnight glucose control

At 23:00, plasma glucose levels were higher during closed-loop; 6.8 mmol/l versus 5.6 mmol/l; $p = 0.041$ (Table 4.2). Nonetheless, the overnight plasma glucose time in target was strikingly high on both closed-loop and CSII visits; 95% versus 100%, $p = 0.484$. Of note, using sensor glucose measurements, there was significantly less time spent in target overnight during CSII; 98% versus 83%, $p = 0.034$ (Table 4.3). There was no discordance between plasma and CGM measurements for other secondary outcomes.

#### 4.5.2.3 Glucose control during exercise

Mean plasma glucose concentrations during the afternoon activities, which included a 20 minute low intensity walk and 55 minutes of brisk walking on a treadmill (following an eight minute step test to calibrate the Actiheart at 13:00), were comparable on closed loop and CSII visits (5.5 mmol/l versus 4.9 mmol/l; $p = 0.270$), with identical time spent in target range (75%; $p = 0.657$), in hyperglycaemia (0%; $p = 0.575$), and in hypoglycaemia (16%; $p = 0.866$). The afternoon period was associated with the highest proportion of hypoglycaemia compared with the evening, overnight and morning periods, for both closed-loop and CSII visits (Table 4.4).

During the evening following dinner (18:00-23:00), time in target was similar between interventions (75% versus 78%, $p = 0.530$). Closed-loop reduced the time spent below 3.5 mmol/l (1% versus 9%; $p = 0.022$), with a greater time spent above 7.8 mmol/l although this was not significant (12% versus 0%; $p = 0.441$).

In the morning, following breakfast and exercise (20 minute walk and 55 minute treadmill session), plasma glucose levels were higher, but comparable between visits (6.8 mmol/l versus 7.0 mmol/l; $p = 0.875$). Despite the morning physical activity being very similar to that performed the prior afternoon, time in target was much lower with one third of the time spent in hyperglycaemia. These outcomes were not different between closed-loop and CSII; time in target 67% versus 63% ($p = 0.929$), time in hypoglycaemia 1% versus 2% ($p = 0.398$), and time in hyperglycaemia 30% versus 29% ($p = 0.638$).

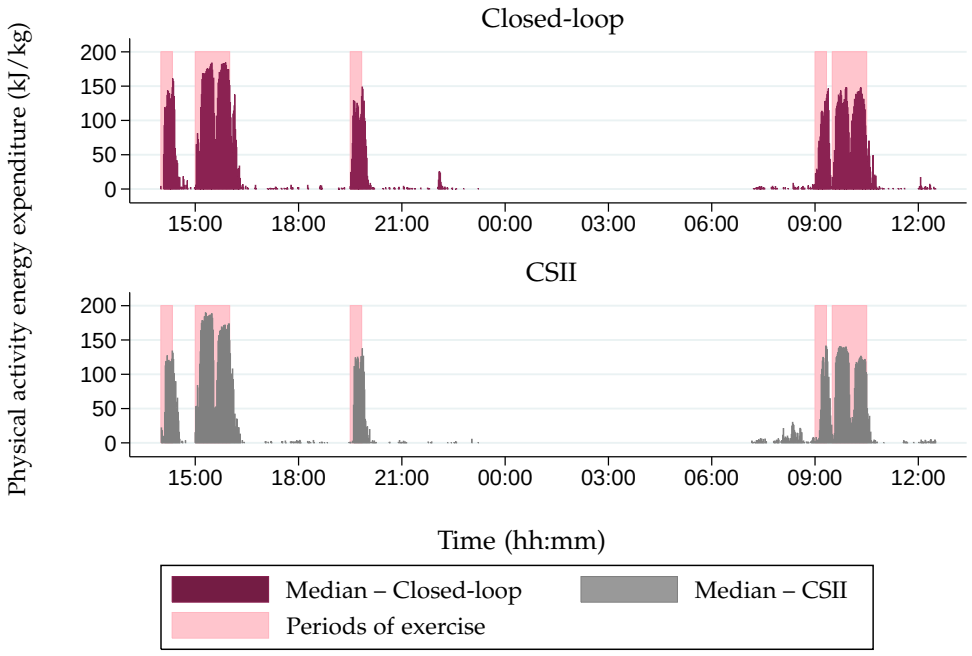
Importantly, physical activity energy expenditure (PAEE) was comparable between closed-loop and CSII visits indicating similar level of activity; 23.4 (19.7, 27.0) versus 21.2 (19.0, 22.1) kJ/kg/day ($p = 0.090$). Figure 4.6 shows PAEE during the overall study on both visits. The peaks correspond to the low (20 minute gentle walks after meals) and moderate (55 minutes brisk treadmill walking at 15:00 and

Table 4.4: Plasma glucose outcomes during closed-loop and CSII for afternoon, evening and morning periods

| | Afternoon (14:00-18:00) | | | Evening (18:00-23:00) | | | Morning (07:30-12:30) | | |
|---|---|---|---|---|---|---|---|---|---|
| | CL | CSII | P-value | CL | CSII | P-value | CL | CSII | P-value |
| Mean plasma glucose (mmol/l) | $5.5 \pm 1.5$ | $4.9 \pm 0.9$ | 0.270 | $6.5 \pm 1.4$ | $5.5 \pm 1.4$ | 0.140 | $6.8 \pm 1.6$ | $7.0 \pm 1.6$ | 0.875 |
| $3.5 <$ Plasma glucose $\leq 7.8$ mmol/l (%) | 75 (64, 84) | 75 (60, 96) | 0.657 | 75 (39, 99) | 78 (67, 89) | 0.530 | 67 (35, 78) | 63 (45, 85) | 0.929 |
| Plasma glucose $\leq 3.5$ mmol/l (%) | 16 (2, 26) | 16 (0, 27) | 0.575 | 1 (0, 5) | 9 (3, 19) | 0.022* | 1 (0, 19) | 2 (0, 14) | 0.398 |
| Plasma glucose $> 7.8$ mmol/l (%) | 0 (0, 12) | 0 (0, 18) | 0.866 | 12 (0, 61) | 0 (0, 16) | 0.441 | 30 (14, 41) | 29 (11, 42) | 0.638 |
| Insulin infusion (U/h) | 0.4 (0.2, 0.9) | 0.5 (0.4, 0.9) | 0.480 | 0.7 (0.5, 1.0) | 0.7 (0.5, 1.2) | 0.480 | 0.8 (0.4, 1.1) | 0.6 (0.4, 1.2) | 0.388 |

**Notes**: Data are mean $\pm$ standard deviation or median (interquartile range). * Denotes statistical significance at the 5% level.

Figure 4.6: Physical activity energy expenditure during closed-loop and CSII




09:30) intensity physical activity with very minimal activity in between scheduled exercise. The median Borg score was 10 and 9 during the afternoon and morning exercise, respectively, with a range from 7 to 15. These scores indicate that the effort of exercise was perceived as 'very light' overall (Figure 4.3).

#### 4.5.2.4 Hypoglycaemia

There were 33 episodes of hypoglycaemia ($\leq$ 3.0 mmol) requiring treatment over 24 study visits. Of the total, 20 episodes were between 2.5 mmol/l and 3.0 mmol/l and 25 episodes were symptomatic. The episodes of hypoglycaemia are shown in Figure 4.4. No episodes required intravenous dextrose treatment. Only two women completed both 24 hour study visits without experiencing any hypoglycaemia. Of the visits on which hypoglycaemia occurred, almost half were associated with multiple episodes, with one subject having five events during her CSII visit.

Overall, there were 13 episodes of hypoglycaemia during closed-loop and 20 dur-

Table 4.5: Summary of hypoglycaemia episodes

| | Afternoon (14:00-18:00) | | Evening (18:00-23:00) | | Overnight (23:00-07:30) | | Morning (07:30-12:30) | | Overall (14:00-12:30) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | CL | CSII | CL | CSII | CL | CSII | CL | CSII | CL | CSII |
| $2.5 <$ Plasma glucose $\leq 3.0$ mmol/l | 3 | 5 | 1 | 2 | 1 | 2 | 3 | 3 | 8 | 12 |
| $2.0 <$ Plasma glucose $\leq 2.5$ mmol/l | 3 | 4 | 0 | 1 | 0 | 0 | 2 | 0 | 5 | 5 |
| Plasma glucose $\leq 2.0$ mmol/l | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 3 |
| Total | 6 | 10 | 1 | 3 | 1 | 3 | 5 | 4 | 13 | 20 |

**Notes**: Data are number of episodes.

ing CSII (Table 4.5). There were three episodes $\leq$ 2.0 mmol/l, all of which occurred during CSII visits.

The majority of hypoglycaemia occurred following moderate intensity exercise (25 episodes) with 16 during afternoon and nine during morning exercise sessions. Eleven episodes occurred even with ingestion of a larger snack (30g carbohydrate) prior to exercise.

Of the total 33 hypoglycaemic episodes, 24 occurred in the first six subjects. Following amendment of the study protocol to include additional 15g carbohydrate snacks in the middle and at the end of exercise sessions for capillary glucose $\leq$ 6.0 mmol/l, there were only nine episodes occurring in the remaining six subjects. All of the hypoglycaemic episodes requiring more than 15g rescue carbohydrate occurred prior to the study protocol amendment (four during closed-loop and three during CSII).

During the overnight period, there were four hypoglycaemic episodes, three of which occurred in the two women who also experienced multiple events during the daytime. Three occurred before midnight: one during closed loop (23:30) and two during CSII (23:15 and 23:40). After midnight, there was one episode of hypoglycaemia during CSII at 03:00.

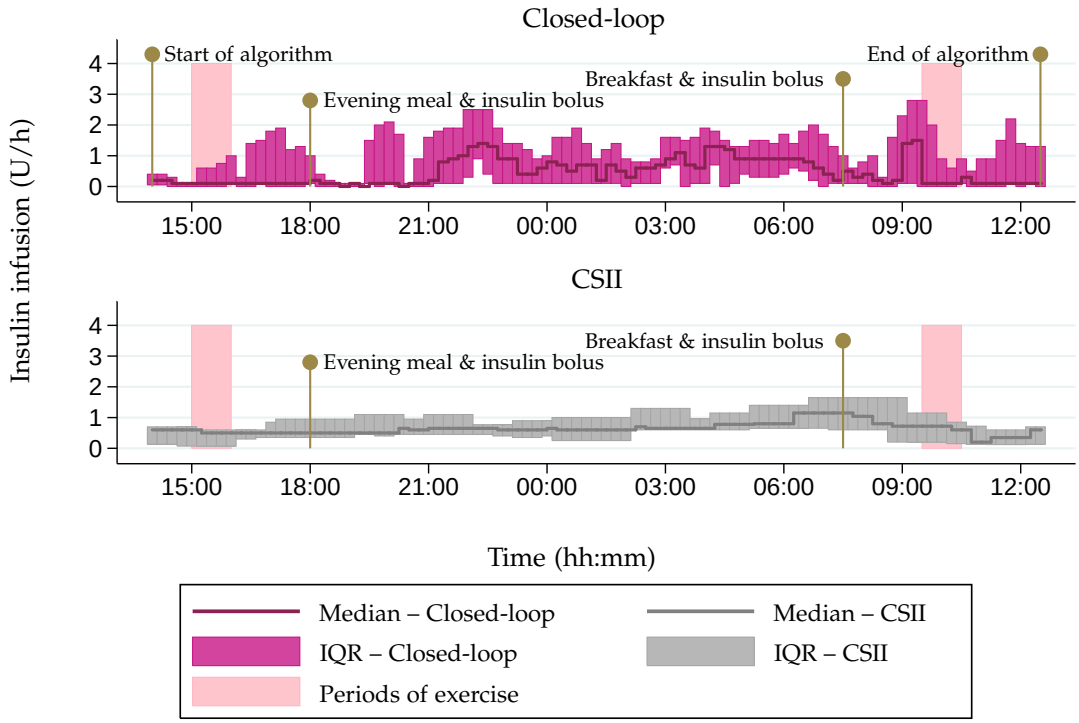
#### 4.5.2.5 Meals and insulin

Average insulin infused did not differ between closed-loop and CSII; 0.7 U/h versus 0.8 U/h, $p = 0.347$ (Table 4.2). Figure 4.7 shows the median basal insulin infused. Individual insulin profiles are given in Appendix A. Considering individual time periods, infusion rates were similar between visits, with the lowest rates seen during the afternoon involving moderate intensity exercise on both interventions (Table 4.4). Basal infusion during closed-loop was minimal following the evening meal from 18:00 until 19:30 (Figure 4.7).

Baseline insulin doses, prandial boluses and quantity of carbohydrates consumed for snacks are summarised in Table 4.6. Two women used complex boluses (dual or square wave) for meals, whilst the remainder used normal boluses. Meal boluses were generally larger during closed-loop despite women using the same method for bolus calculation and consuming identical meals on both closed-loop and CSII visits.

A minority of women had correction boluses of insulin with snacks: one before afternoon exercise, three at bedtime, and four women corrected before morning exercise. The total quantity of snacks consumed for afternoon exercise ranged from

Figure 4.7: Insulin infusion rates during closed-loop and CSII




15 – 75g carbohydrate, with at least 45g carbohydrate required on nine (of the total 24) occasions. During the morning exercise, carbohydrates consumed ranged from 0 – 60g (snack declined on two occasions based on capillary glucose testing after breakfast), with 45g or more carbohydrate required on three visits.

Measured plasma insulin concentration was similar between interventions; 120 pmol/l versus 107 pmol/l, $p = 0.875$ (Table 4.2). A higher median peak plasma insulin concentration was seen following meals during closed-loop, which may be related to the larger boluses taken for dinner and breakfast (Figure 4.8). Another reason may be the marked decrease in basal rates after the evening meal under model predictive algorithm control resulting in apparently more pronounced peak insulin levels.

In the morning after breakfast, a second peak in plasma insulin concentration was observed during closed-loop (Figure 4.8) with a corresponding higher insulin

Table 4.6: Summary of insulin amounts and carbohydrates consumed

| | Closed-loop | | CSII | |
|---|---|---|---|---|
| | Median | IQR | Median | IQR |
| *Pre-study* | | | | |
| Total daily insulin (U) | 53.2 | (35.4, 73.4) | 54.1 | (33.7, 70.9) |
| Total daily bolus (U) | 31.2 | (24.0, 39.6) | 24.9 | (23.1, 49.3) |
| Total daily basal (U) | 20.1 | (15.6, 29.8) | 17.8 | (13.8, 20.3) |
| Total daily insulin/kg (U) | 0.7 | (0.5, 0.9) | 0.7 | (0.5, 0.9) |
| *During study* | | | | |
| Lunch carbohydrate (g)[a] | 50 | | 50 | |
| Lunch bolus (U) | 7.2 | (5.0, 10.8) | 6.5 | (4.9, 10.0) |
| Afternoon snack carbohydrate (g)[b] | 30 | (30, 58) | 32 | (16, 60) |
| Afternoon snack bolus (U) | 0.0 | (0.0, 0.0) | 0.0 | (0.0, 0.0) |
| Dinner carbohydrate (g)[a] | 60 | | 60 | |
| Dinner bolus (U) | 8.6 | (5.6, 11.5) | 7.1 | (4.7, 11.1) |
| Bedtime snack carbohydrate (g)[b] | 15 | | 15 | |
| Bedtime snack bolus (U) | 0.0 | (0.0, 0.4) | 0.0 | (0.0, 1.1) |
| Breakfast carbohydrate (g)[a] | 50 | | 50 | |
| Breakfast bolus (U) | 8.0 | (5.7, 10.6) | 6.3 | (3.8, 8.9) |
| Morning snack carbohydrate (g)[b] | 15 | (15, 18) | 15 | (15, 30) |
| Morning snack bolus (U) | 0.0 | (0.0, 0.0) | 0.5 | (0.0, 2.1) |

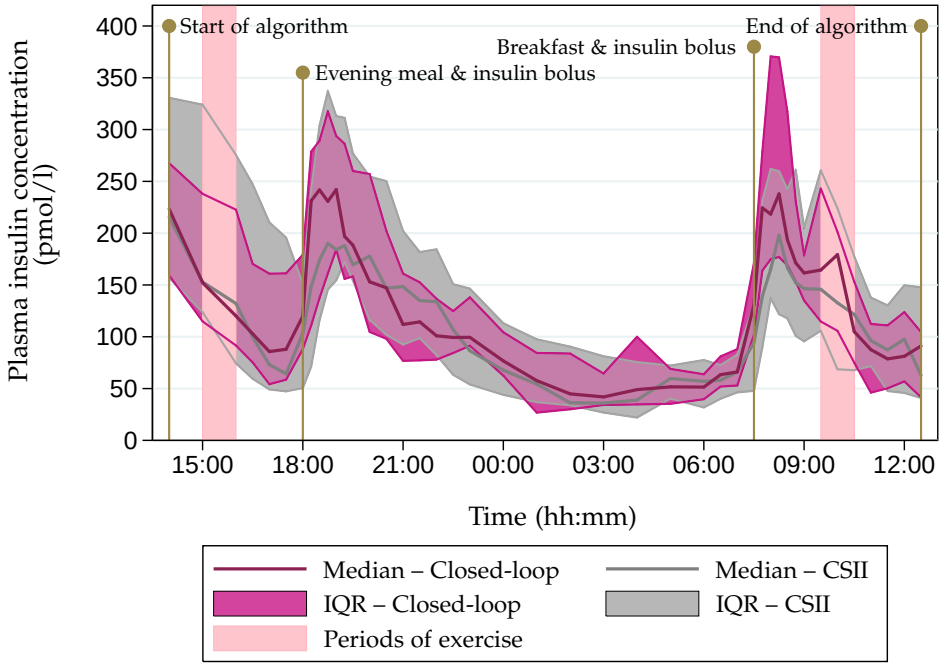
**Notes**: [a] Size of meal identical across subjects, on closed-loop and CSII visits; [b] size of snack varied according to capillary glucose readings prior to, and during, exercise.

delivery (Figure 4.7), most likely due to rising glucose following the pre-exercise snack. Importantly, this increased insulin delivery was not associated with a greater risk of hypoglycaemia post exercise (Table 4.5). Additionally, no correction boluses were required on closed-loop compared with 0.5U on CSII (Table 4.6).

### 4.5.3 Sensor accuracy

The median relative absolute difference between the FreeStyle Navigator (Abbott Diabetes Care, Alameda, CA, USA) sensor and reference plasma glucose measurements was 13.3%. This is higher than previously reported in a closed-loop study in pregnant women with type 1 diabetes carried out under sedentary conditions (11.4%),[108] and is most likely related to daytime glucose fluxes with meals and physical activity. The Clarke error grid analysis in Figure 4.9 illustrates the relationship between sensor and reference glucose values, showing the majority of values in zones A and B, with

Figure 4.8: Plasma insulin concentration profiles during closed-loop and CSII



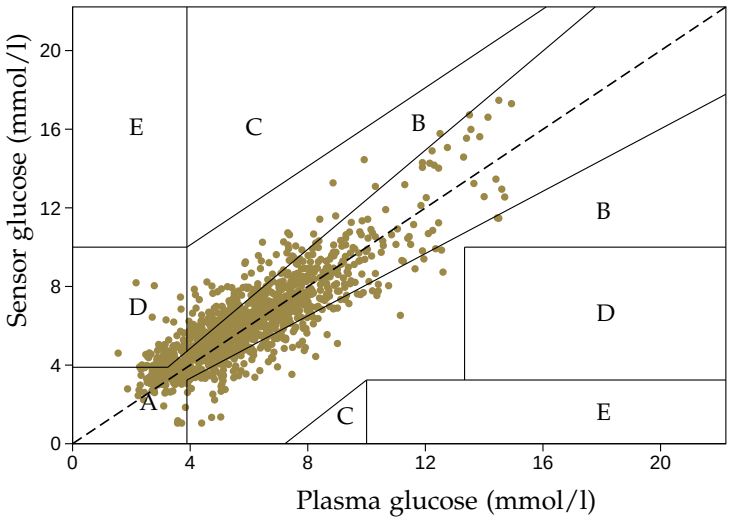

a smaller proportion in zone D.

## 4.6 Discussion

This is the first randomised crossover study of closed-loop in pregnancy, evaluating women with type 1 diabetes during normal daily activities. This study aimed to replicate a typical day at home or work including consumption of regular meals and snacks, and scheduled low and moderate intensity activity. Closed-loop was as effective as conventional insulin pump therapy, with 81% of time spent with glucose levels in the recommended range for pregnancy ($3.5 - 7.8$ mmol/l).[94] The lack of difference between interventions is likely due to the optimally-controlled cohort of women studied (baseline HbA1c 6.4%).

In comparison with the overnight period, optimal daytime glycaemic control is significantly more challenging. A previous study in pregnant women with type 1 diabetes evaluated overnight closed-loop under sedentary conditions demonstrating

Figure 4.9: Clarke error grid analysis showing accuracy of FreeStyle Navigator CGM




**Notes:** Values in zone A or B are clinically acceptable. Values in zone C, D or E are potentially unsafe.

84% and 100% time in target during early and late gestation, respectively.[108] As the closed-loop adjusts basal insulin infusion rates alone, it is likely to have less of an impact during the daytime when $45-60\%$ of insulin was delivered as boluses for meals. In addition, the increasing ratio of bolus to basal insulin with advancing gestation may further limit the influence of closed-loop insulin delivery.

No additional insulin infusion was required during closed-loop. Excess insulin therapy may result in unnecessary weight gain, which may be associated with adverse obstetric outcomes during pregnancy.[54]

Of note, women did not have access to CGM during either visit, hence adjustments for exercise and meals were made using fingerprick glucose alone, without input from the study clinicians. During CSII visits when usual pre-programmed basal rates were continued, mean glucose was 5.8 mmol/l and women achieved 81% time in target.[108] These values represent substantially better glycaemic control than previously reported from free-living studies using CGM in pregnancy.[223] Although the study was designed to be as realistic as possible, the laboratory setting may have had an influence on the improved glycaemic control seen. One possible reason is

that women were motivated and had more time to engage in their diabetes care, in contrast to the home situation where work and family commitments may take precedence. Nonetheless, glycaemic targets were achieved with existing strategies including carbohydrate counting, fingerprick glucose testing and conventional insulin pump therapy.

### 4.6.1 Postprandial periods

Postprandial hyperglycaemia was observed during both closed-loop and CSII visits, particularly following breakfast when approximately 30% of time was spent above target ($> 7.8$ mmol/l). Similar elevated glucose levels ($28 - 44$% above target) following a 60g-carbohydrate breakfast were seen in a previous feasibility study of closed-loop in pregnancy.[108] Use of stable isotope tracers demonstrated time to appearance of half the glucose from the sugar-rich breakfast of 58 minutes, compared with 109 minutes for the starch-rich evening meal in addition to a second peak two to four hours later.[224] These results indicate faster absorption of sugar-rich meals, which may explain the steep rise in glucose levels after breakfast during my study.

The quantity and type of meals provided may have differed from womens' usual diet. In gestational diabetes, reduction in total daily carbohydrate intake in addition to preferential consumption of low glycaemic index carbohydrates may improve glycaemic control.[144] In my study, all meals complied with American College of Obstetricians and Gynaecologists guidelines comprising $40 - 50$% carbohydrates, 20% protein and $20 - 30$% fat, although the glycaemic index of carbohydrates consumed was not considered.[225]

Prandial insulin doses were calculated using womens' usual bolus wizard calculators during both interventions. Inaccurate estimation of the meal bolus, for example due to incorrect pre-programmed insulin to carbohydrate ratios, may have contributed to the rise in glucose levels following meals. Another reason may be a delay in insulin absorption, over and above that seen outside of pregnancy, which may be related to increasing insulin resistance with advancing gestation. Time to peak insulin concentration following meals was 49 minutes during early and 71 minutes during late gestation in a study of women with type 1 diabetes.[224] These results suggest that administration of insulin at least $15 - 30$ minutes before meals may be required to overcome the delays in insulin absorption during pregnancy. In my study, insulin boluses were administered 10 minutes prior to meals, unless fingerprick glucose was below 4.0 mmol/l. Importantly, these strategies to improve daytime glycaemic con-

trol can be implemented using conventional insulin therapy. A closed-loop system with meal announcement, as employed in this study, may overcome the discrepancy between rapid appearance of meal-derived glucose in the bloodstream and delayed absorption of subcutaneously delivered insulin.

### 4.6.2 Exercise

Compared with conventional CSII, closed-loop reduced the frequency of hypoglycaemic episodes (13 versus 20) and the low blood glucose index. Several factors may influence glycaemic control with exercise. The majority of hypoglycaemia episodes were associated with moderate intensity exercise despite anticipatory 15g carbohydrate snacks, or 30g for fingerprick glucose below 6.0 mmol/l. This is similar to the American Diabetes Association recommendation of additional carbohydrates for glucose less than 5.6 mmol/l prior to physical activity.[226] Exercise was delayed if capillary glucose was below 4.0 mmol/l, comparable to the American Diabetes Association guideline of 4.4 mmol/l. The inclusion of additional $15-30$g carbohydrate snacks during and at the end of exercise reduced the occurrence of hypoglycaemia. The composition of the snacks consumed (high versus low glycaemic index) are likely to have had a variable effect on glucose control, although this was not specifically evaluated.

During CSII visits, women set temporary basal rates for exercise according to their usual practice, using capillary blood glucose levels alone. During closed-loop visits, information on exercise timing and duration was announced to the algorithm one hour prior to exercising. Although the model predictive control algorithm used is updated continuously in real-time, rapid changes in glucose levels during exercise may lead to delays in glucose sensing in interstitial fluid and subsequent delays in appropriate adjustment of insulin infusion rates. Compared with CSII visits, closed-loop basal insulin delivery was minimal during and following both exercise sessions, suggesting the prandial insulin dose had a greater effect (Figure 4.7). Although the majority of women reduced their prandial insulin bolus prior to exercise, this was estimated using their usual bolus calculators, and hence may not have been enough to prevent a decline in glucose levels. A study in non-pregnant adults with type 1 diabetes evaluated the effect of exercise performed 90 minutes after administration of an insulin bolus for a 48g carbohydrate breakfast, similar in design to the morning exercise in my study.[227] Both a 50% reduction in pre-meal insulin and pump suspension during exercise were required to prevent hypoglycaemia.

The physical activity performed in my study was of low to moderate intensity, which is associated with a greater risk of hypoglycaemia.[187] This may be one reason for the hypoglycaemia observed. Additionally, the scheduling of exercise within two to three hours of the antecedent mealtime insulin bolus is likely to have had an effect on the observed glycaemic responses. As the duration of action of rapid acting insulin is up to four hours, the prandial insulin bolus was likely to have had an effect on glycaemic control at the time of exercising.

The frequency of hypoglycaemic episodes was much higher for afternoon compared with morning exercise (16 versus 9 episodes). This may have been due to greater energy expended in the afternoon prior to the treadmill exercise including an eight minute step test to calibrate the Actiheart and effort expended in arriving to the study visits (e.g. walking from the car park and carrying an overnight bag). A previous study showed a higher risk of hypoglycaemia when exercise was undertaken in the afternoon compared with the morning.[228] The occurrence of hypoglycaemia in the afternoon on closed-loop visits may be related to inadequate time for the algorithm to establish optimal glycaemic control, as it was commenced only one hour prior to exercise. Previous studies in children using the same algorithm demonstrated improving performance of closed-loop with longer duration of use.[104]

Late afternoon exercise may be associated with an increased risk of nocturnal hypoglycaemia.[194; 195] In my study, glucose levels were in target range for $95-100\%$ of the overnight period, with 0% time in hypoglycaemia during both interventions. There were no episodes of hypoglycaemia during closed-loop after midnight. Following the evening meal, closed-loop provided safer glucose control with significantly less time spent in hypoglycaemia. Additionally, the higher plasma glucose at bedtime (23:00) during closed-loop (6.8 mmol/l versus 5.6 mmol/l during CSII) may be a safer glucose concentration to minimise risk of hypoglycaemia overnight. Blood glucose $< 6$ mmol/l was the strongest predictor of nocturnal hypoglycaemia in a study in women with type 1 diabetes during early pregnancy.[229]

Both prior exercise and hypoglycaemia may impair the counter-regulatory response to subsequent exercise with ensuing increased risk of hypoglycaemia.[196; 197] Except for two episodes (occurring in the same subject), all of the episodes of morning hypoglycaemia occurred in women who had experienced hypoglycaemia the day prior. Similarly, any hypoglycaemia prior to arrival for study visits may have increased the risk of later episodes during the study period.

### 4.6.3 Strengths and limitations

The study was designed to approximate a real-life setting with normal daily activities including exercise, meals and snacks. This was in preparation for testing the closed-loop system in the home environment where patients are faced by such challenges on a daily basis. The exercise performed was achieved without any discomfort, with the perceived level of exertion reported as light or very light. Importantly, the 24-hour study period enabled evaluation of the effect of exercise on glucose levels over a longer duration, including overnight. Activities were matched on both visits to enable direct comparison of glucose control between interventions, and an objective measure of physical activity energy expenditure was used.

Women were able to select from at least four choices for meals and eight choices of snacks, thus simulating the range of foods that might be consumed at home, in addition to evaluating the ability of the control algorithm to cope with foods of varying macronutrient content. One limitation of standardising the meals was that the women were required to eat the specified amount, regardless of whether that was consistent with their usual practice. This may have contributed to the higher glucose levels seen following breakfast, as a large proportion of the women reported that they often consume fewer carbohydrates for breakfast at home. The glycaemic index of the snacks consumed for exercise, which is likely to have a differential effect on glucose levels, was not ascertained.

Despite trying to mimic normal daily activities as closely as possible, large parts of the study visits were spent reclining in bed which is not representative of outpatient life, and highlights one of the limitations of clinic-based research.

All of the women studied had very well controlled diabetes at baseline, which is likely to have an effect on the degree of hypoglycaemia and hyperglycaemia observed. This may have been because women who are more motivated and engaged in the management of their diabetes are more likely to volunteer to take part in research. Evaluation of women with suboptimal glycaemic control is warranted, as this cohort is likely to derive a benefit from closed-loop insulin delivery.

## 4.7 Conclusion

In conclusion, in this cohort of well controlled women with type 1 diabetes during pregnancy, closed-loop insulin delivery was as effective as conventional pump therapy during a typical day including meals, snacks and physical activity. Moderate

intensity exercise was undertaken on consecutive days without any discomfort. Hypoglycaemia was common following exercise sessions during both interventions, but closed-loop prevented nocturnal episodes. The effectiveness of closed-loop may be lower in the daytime when a relatively higher proportion of total daily insulin is attributed to boluses. This effect may be even more pronounced during pregnancy, due to the increasing ratio of bolus to basal insulin with advancing gestation. Even with conventional insulin pump therapy guided by fingerprick glucose tests alone, women achieved 80% overall and 100% overnight time in target glucose, suggesting those who are motivated can achieve optimal glycaemic control with the currently available strategies.

# Chapter 5

# Energy expenditure and glucose control in pregnancy

## 5.1 Background

### 5.1.1 Exercise in type 1 diabetes

#### 5.1.1.1 Benefits

Regular physical activity in healthy individuals is associated with several physiological gains, including improved cardiovascular fitness, body composition, blood pressure and lipid profiles.[230] In addition, exercise has been shown to increase insulin sensitivity and lower the incidence of new diabetes.[231]

In a cohort study of 500 people with type 1 diabetes, there was a significant inverse relationship between activity levels and occurrence of diabetes-related complications as well as mortality risk at seven years follow up.[232] Although the cardiovascular benefits of exercise in type 1 diabetes are well known, there is less evidence of an improvement in glycaemic control. Reduced insulin requirements and/or the increased caloric intake required to prevent exercise-induced hypoglycaemia are possible explanations for a masking of improvement in glucose control.

#### 5.1.1.2 Targets

Despite awareness of the positive effects of exercise, activity levels amongst patients with type 1 diabetes remain low, largely due to the challenges in maintaining normal glucose levels and avoiding hypoglycaemia.[233] This risk is even greater during

pregnancy due to increased energy demands placed by the foetus as well as the tighter glycaemic targets necessitated to avoid hyperglycaemia-related adverse foetal and obstetric outcomes.[176]

For healthy adults, the American College of Sports Medicine recommends a minimum of 30 minutes of moderate intensity exercise such as brisk walking five days a week, in addition to 20 minutes of vigorous aerobic activity such as jogging three days a week, and resistance training and neuromotor exercises at least two days a week.[230] The American Diabetes Association position statement declares that 'all levels of physical activity, including leisure, recreational and competitive sports, can be performed by people with type 1 diabetes who do not have complications and are in good blood glucose control'.[226] The American College of Obstetricians and Gynaecologists published guidelines for exercise in pregnancy in 2002, recommending at least 30 minutes of exercise on most days of the week in otherwise healthy pregnant women. In those with type 1 diabetes, prior medical evaluation is indicated only for those with poor control.[234]

#### 5.1.1.3 Relationship with glucose control

With the wider availability of CGM and accelerometry, increasing efforts are being made to understand the relationship between physical activity and glycaemic control. A significant correlation ($0.58 - 0.99$) was seen in six (of a total 16) children with type 1 diabetes, monitored with a physical activity sensor (Diatrace) and CGM for up to three days.[235] Evaluation in 11 adults with type 1 diabetes during 30 minutes of exercise failed to demonstrate a correlation between declining plasma glucose levels and increasing heart rate and accelerometry counts.[236]

#### 5.1.1.4 Measuring physical activity

There is a lack of data on physical activity energy expenditure (PAEE) during pregnancy. A major limitation of studies evaluating exercise is the reliance on subjective self-reporting methods, which are confounded by misreporting and a tendency to overestimate energy expenditure.[237] The International Physical Activity Questionnaire under-predicted less intense and over-predicted more intense activity in a study in healthy women during pregnancy, compared with more objective methods.[238] The gold standard for measuring energy expenditure under free-living conditions is the doubly-labelled water technique.[239] This method is however expensive and time consuming and does not provide information on the frequency and intensity of

physical activity, which may be better assessed by pedometers (less sensitive during upper body exercise) or accelerometry.

Accelerometers are portable motion sensors which have been validated against the doubly-labelled water method in non-pregnant populations.[240] A wrist-worn tri-axial accelerometer failed to provide a reliable measurement of PAEE in pregnancy when compared with non-pregnant women.[241] Accelerometry alone may underestimate PAEE due to its limited ability to detect lower levels of physical activity as occurs in late gestation.[237; 242] Heart rate is directly related to oxygen consumption, but on its own may not be an accurate measure of PAEE during low intensity activity when changes in heart rate are less pronounced, and may be confounded by factors which increase resting heart rate such as stress and pregnancy itself. Use of combined heart rate and accelerometry monitoring may provide a better estimation of PAEE.[243] One such device is the Actiheart (Cam Ntech Ltd, Papworth, UK) which has been employed in two studies in pregnancy to date.[244; 245]

### 5.1.2 Exercise in pregnancy

During pregnancy, additional benefits of exercise include limitation of excess maternal weight gain, fewer delivery-related complications, as well as an improved foetal stress response and reduced fat mass.[246] Regular moderate to high intensity cycle training in healthy pregnant women attenuated the rise in insulin resistance normally seen with increasing gestation.[247] The benefits of exercise on weight, fat mass and cardiovascular profiles have been shown to be maintained several years after pregnancy.[248]

Although the beneficial effects of exercise are widely accepted, the majority of studies evaluating the effect of physical activity in diabetic pregnancy have been carried out in women with or at risk of gestational diabetes mellitus, demonstrating improved insulin sensitivity and better glycaemic control.[249; 250]

There is no objective data on physical activity in pregnant women with type 1 diabetes. Only one study, carried out over 25 years ago, evaluated the effect of a postprandial walking programme in this patient group, showing an improved lipid profile with no difference in glycaemic control.[251]

Physical activity levels are lower in pregnancy and decline with advancing gestation, compensating for the increased energy cost of exercise.[217] Total energy expenditure, which is a composite measure of basal metabolic rate ($60-75\%$), diet-induced thermogenesis (10%) and activity energy expenditure ($25-30\%$), is increased. This

is due to a 20% higher basal metabolic rate in pregnancy, attributed to accelerated fat and protein synthesis, increased tissue mass and increased overall metabolic load, all of which increase with advancing gestation.[219]

Longitudinal assessment of physical activity using accelerometry and self-report questionnaires in overweight pregnant women in England found that over 60% achieved the minimum recommended 30 minutes of moderate intensity activity daily, which was maintained throughout gestation.[252] Another UK study evaluating 64 normal weight women using a multi-axial accelerometer demonstrated a progressive decline in physical activity levels with advancing gestation.[242] The accelerometer used was less accurate at detecting the low levels of activity more common in late pregnancy, and compliance with wear also declined over time.

A study using a multi-axial accelerometer, doubly labelled water and indirect calorimetry in pregnant women in Sweden showed that 63 minutes per day (4%) was spent in moderate activity.[253] Compared with non-pregnant women, 92 more minutes was spent on sedentary activity with 94 minutes less on standing and walking, in addition to choosing a slower pace. In another Swedish study, physical activity patterns were evaluated in healthy and overweight women using a combined heart rate and movement sensor, doubly-labelled water and indirect calorimetry.[245] Compared with controls, pregnant women spent 13% more time sedentary and 71% less time in moderate-vigorous intensity activity. Despite 44% lower total activity levels, pregnant women achieved a similar exercise-related improvement in insulin sensitivity. Accelerometry and indirect calorimetry assessment of energy expenditure in 27 healthy Swiss women showed a 20% higher resting metabolic rate, accounting for the increase in total energy expenditure during late pregnancy compared with postpartum.[244] PAEE, adjusted for body weight, was lower during pregnancy with more time spent in less intense activities.

### 5.1.3 Glucose control in pregnancy

#### 5.1.3.1 Targets

Recommended glycaemic targets for pregnant women with diabetes are fasting glucose between $3.5 - 5.9$ mmol/l and one hour-postprandial level below 7.8 mmol/l.[94] Continuous glucose monitoring (CGM) profiles recorded in 57 healthy women during pregnancy demonstrated mean fasting glucose of 4.2 mmol/l and postprandial peak glucose of 6.1 mmol/l.[254] These glucose profiles are significantly lower than the levels currently recommended for women with diabetes, suggesting that tighter

glycaemic targets levels may be required to reduce the risk of adverse maternal and foetal outcomes.[255] In a study of 12 CSII-treated pregnancies, despite maintaining strict glycaemic targets with mean Hba1c 6.5%, 5.9% and 5.8% in trimesters 1, 2 and 3 respectively, mean birth weight was still increased with large for gestational age infants in 35%.[256] It is suggested that a mean glucose of 5.3 mmol/l or lower throughout the second and third trimesters may be required to achieve normal foetal growth.[257]

#### 5.1.3.2 Evidence from CGM

The emergence of CGM over the last decade has revolutionised the monitoring of diabetes. Its use in pregnancy may be especially valuable in detecting the dynamic glucose excursions that occur with the physiological changes of advancing gestation. Evidence of CGM use in pregnancy is increasing. The high day to day glucose variability was shown in a study of pregnant women with type 1 diabetes using CGM for two days.[258] Another study observed a mean time spent in hyperglycaemia ($>$ 7.8 mmol/l) of 192 minutes/day, not detected by SMBG.[259] Nocturnal hypoglycaemic events ($<$ 2.8 mmol/l) occurred in 26 of the 34 women (76%), one-third of whom did not experience any symptoms. Assessment of glycaemic control using retrospective CGM worn in each trimester showed that women with type 1 diabetes spent only 43% of the day in euglycaemic range ($3.9 - 7.8$ mmol/l) in the first trimester during which critical foetal development occurs, improving to only 56% by the third trimester.[223] Almost 33% time was spent hyperglycaemic, while time spent in hypoglycaemia was 14% overall and 16% overnight.

A randomised trial of intermittent retrospective CGM use (worn for up to seven days, at four to six week intervals) in 71 women with pregestational diabetes provided evidence of a benefit of CGM on clinical outcomes.[215] Compared with standard antenatal care, CGM resulted in an improvement in HbA1c in late gestation from 6.4% to 5.8%, lower mean birth weight and reduced risk of macrosomia. A recent study in 25 women evaluating continuous (daily) versus intermittent (14 days per month) real-time CGM from three months pre-conception until delivery, found no difference in maternal and foetal outcomes with both groups demonstrating similar decline in HbA1c from first to third trimester.[260]

## 5.2 Rationale

The relationship between physical activity and glucose levels is multifactorial, further complicated by the unique physiology of pregnancy. There is no objective evidence on physical activity patterns or energy expenditure in pregnant women with type 1 diabetes. Several previous studies have evaluated glycaemic control using CGM in mixed groups of women, including those with type 1 and 2 diabetes and on both MDI and CSII. None have used CGM in a cohort of women exclusively on CSII. Furthermore, none have studied the effects of controlled diet and exercise on glucose levels. Detailed evaluation of PAEE and glycaemic control may contribute to the development of evidence based guidelines for optimising diabetes management during pregnancy.

## 5.3 Aim

The aim of this study was to objectively investigate physical activity energy expenditure and glucose control as measured by continuous glucose monitoring, in pregnant women with type 1 diabetes during free-living and structured diet and exercise conditions.

## 5.4 Methods

### 5.4.1 Study design

As part of the study evaluating closed-loop insulin delivery in pregnancy described in Chapter 4, activity patterns and glucose levels in ten women with type 1 diabetes were investigated, under free-living and controlled study conditions.

#### 5.4.1.1 Controlled diet and exercise conditions

Women attended a clinical research facility from midday until 12:30 the following day. Activities of varying intensity, measured in metabolic equivalents (METs), were planned over the 24-hour study period, based on reference values.[261] The study protocol included scheduled low (three 20-minute self-paced walks after meals) and moderate (two 55-minute sessions of brisk treadmill walking, each with a 5 minute rest interval) intensity exercise. The Borg rating of perceived exertion was used to assess effort level during exercise (Figure 4.3).[220] In between scheduled exercise,

women undertook sedentary tasks such as working on a computer, watching television or reading.

Participants were given standardised $50-60$g carbohydrate meals and a 15g carbohydrate snack before bed. All meals were accompanied by an insulin bolus, calculated using the pump bolus wizard or insulin to carbohydrate ratios. Additional snacks were consumed according to capillary glucose measured prior to, during and after treadmill exercise. Women continued their standard insulin pump regimen, and were able to set temporary basal rates and/or reduce pre-exercise meal insulin boluses.

A FreeStyle Navigator CGM (Abbott Diabetes Care, Alameda, CA, USA) was inserted one to two days prior to the study visit. Women did not have access to CGM readings, and any adjustments to insulin doses were made using capillary glucose measurements. A non-invasive combined heart rate and accelerometer device (Actiheart, Cam Ntech Ltd, Papworth, UK) was individually calibrated for each subject and attached on arrival (Figure 4.2).[216]

#### 5.4.1.2 Free-living conditions

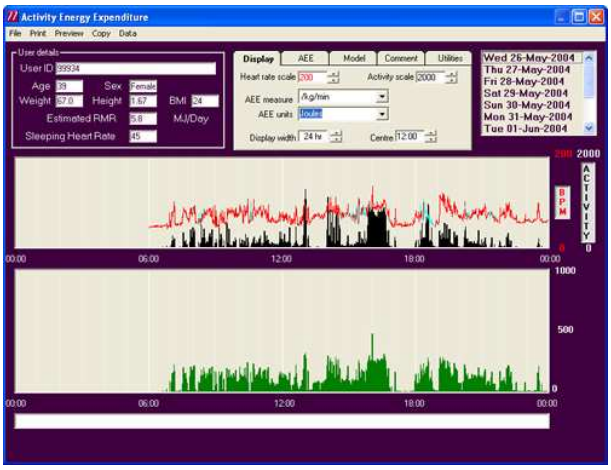
On completion of the controlled study, women were asked to continue wearing both the CGM and acclerometer at home in order to obtain free-living data. Basic training and written instructions on device calibration and interpretation of real-time CGM data (available to women at home) was provided. The Actiheart could be worn continuously throughout out the day and overnight, including whilst bathing. Women were provided with extra electrocardiogram pads to be replaced if the existing ones came loose from the skin due to moisture. During the recording period, women were asked to consume meals and carry out physical activity according to their usual daily routine (ad libitum). To reduce any persisting effect of the controlled study conditions, the first 24 hours of PAEE was not considered for analysis. At the end of the free-living recording period, women returned the Actiheart and CGM devices, which were downloaded retrospectively.

### 5.4.2 Measurements

#### 5.4.2.1 Demographic and anthropometric information

Demographic data was collected at the baseline screening visit. Weight was measured to the nearest 0.1kg using calibrated electronic scales (Kern & Sohn GmbH, Germany)

Figure 5.1: Example of Actiheart recording




and height to the nearest 0.1cm using a calibrated stadiometer (Seca, UK), on arrival to the clinical research facility for the controlled study.

#### 5.4.2.2 Physical activity energy expenditure (PAEE)

PAEE was measured using the Actiheart device (Cam Ntech Ltd, Papworth, UK). An example of the recording is shown in Figure 5.1.

#### 5.4.2.3 Continuous glucose monitoring

The FreeStyle Navigator CGM (Abbott Diabetes Care, Alameda, CA, USA), with a one-hour run-in calibration period and calibrated with capillary glucose measurements, measured sensor glucose.

### 5.4.3 Statistical analysis

PAEE was computed using the Actiheart software programme. Sleeping heart rate, calculated as the highest of the 60 lowest heart rate recordings during a 24 hour period, was used with the step test derived individual calibration parameters to adjust a heart rate-energy expenditure equation. This was then introduced into a branched equation model, combining heart rate and accelerometry, to estimate PAEE.[222] An adjustment was made for diurnal stability and the probability of device wear. Recordings with 50% or lower likelihood of device wear based on combined heart rate and

accelerometry, were excluded.

Proportion of time spent in various activities was described as metabolic equivalents, a concept which expresses the energy cost of physical activity as a multiple of basal metabolic rate where one MET (kcal/kg/hr) equates to resting oxygen consumption, conventionally set at 3.5 ml $O_2$/kg of body weight/min based on an average 70-kg male. Metabolic equivalents can be used as an index of the intensity of physical activity, which was categorised as sedentary ($\leq$ 1 MET), light ($1-3$ METs), or moderate to vigorous ($>$ 3 METs).[261]

Glycaemic outcomes were calculated using sensor glucose for overall (14:00-12:00) and overnight (23:00-07:30) periods. These included time spent within, above and below target glucose defined as $3.5-7.8$ mmol/l, based on National Institute for Health and Clinical Excellence guidelines for pregnancy.[94] Mean glucose, standard deviation of glucose and the low blood glucose index were also calculated.[97] Episodes of hypoglycaemia were quantified during the controlled study.

Values are given as median (interquartile range) or mean $\pm$ standard deviation. Significant differences ($p \leq 0.05$) were identified using non-parametric $t$-tests for paired data. Analyses were conducted using SPSS Version 15 (SPSS Inc, Chicago, IL, USA).

## 5.5 Results

### 5.5.1 Demographic data

Ten women of the original cohort which took part in the closed-loop study completed the free-living phase of the study. The baseline characteristics of these women are summarised in Table 5.1.

### 5.5.2 Activity patterns and energy expenditure

A 22-hour consecutive period of PAEE recordings during free-living at home, matched in time to the controlled study visit (14:00-12:00), was evaluated. Median PAEE during free-living was 15.9 kJ/kg/day with the wide interquartile range (10.8, 22.9) indicating a greater variability in intensity of physical activity at home (Table 5.2). Most of the day was spent sedentary (54%) or in light activity such as standing (43%), with only 2% spent in moderate intensity activity.

During controlled study conditions including structured exercise, PAEE was 21.2 (18.2, 22.4) kJ/kg/day, with 62% of time spent sedentary, 30% in light activity and 8%

Table 5.1: Demographics of 10 participants

| Characteristic | Number of subjects | Mean | Standard deviation |
|---|---|---|---|
| Age (years) | | 33.2 | 3.7 |
| Weight (kg) | | 78.7 | 10.0 |
| BMI ($kg/m^2$) | | 27.9 | 3.3 |
| Diabetes duration (years) | | 16.6 | 9.7 |
| Pump duration (years) | | 2.4 | 2.8 |
| HbA1c (%) | | 6.5 | 0.4 |
| Total daily insulin (U) | | 49.5 | 18.3 |
| Gestation (weeks) | | 19.7 | 5.7 |
| Parity | | | |
| *Nulliparous* | 7 | | |
| *Multiparous* | 3 | | |
| Ethnicity | | | |
| *European* | 10 | | |
| *Other* | 0 | | |
| Current employment status | | | |
| *Full-time ($\geq$ 35 hours/week)* | 7 | | |
| *Part-time ($<$ 35 hours/week)* | 3 | | |
| *Unemployed* | 0 | | |
| Living with partner | | | |
| *Yes* | 10 | | |
| *No* | 0 | | |
| Smoker | | | |
| *Yes* | 0 | | |
| *No* | 10 | | |

in more intense activity. The median Borg score was 10 and 9 during the afternoon and morning exercise, respectively, indicating a 'very light' perceived level of exertion (Figure 4.3). Overall, the minimum rating was 7 with a maximum of 15.

Median PAEE during free-living and controlled study conditions is shown in Figure 5.2. During free-living, the majority of ambulatory time (from 07:30 until 22:30 approximately) was spent in light activity. The highest PAEE was observed between 07:30 and 09:00, while lowest PAEE whilst ambulatory was recorded between 21:00 and 22:30. During the controlled study, significantly higher PAEE was achieved during scheduled exercise. Peak PAEE levels were only slightly higher during moderate intensity brisk treadmill walking (15:00 and 09:30), compared with the low intensity postprandial walks (14:00, 19:30 and 09:00). In between scheduled exercise, PAEE was minimal, indicating that the women were sedentary, except for a short period of light activity in the morning after breakfast corresponding to having a wash and

Table 5.2: Physical activity energy expenditure and time spent in sedentary, light and moderate intensity activity

| | Units | Free-living | Controlled study | P-value |
|---|---|---|---|---|
| Physical activity energy expenditure | kJ/kg/day | 15.9 (10.8,22.9) | 21.2 (18.2,22.4) | 0.241 |
| Sedentary time (MET $= 1$) | % | 54 (47,65) | 62 (59,70) | 0.047* |
| | Minutes | 778 (677,850) | 893 (850,1008) | |
| Time spent in light activity ($1 <$ MET $\leq 3$) | % | 43 (34,49) | 30 (23,33) | 0.005* |
| | Minutes | 619 (490,706) | 432 (331,475) | |
| Time spent in moderate activity (MET $> 3$) | % | 2 (1,5) | 8 (8,10) | 0.022* |
| | Minutes | 27 (14,68) | 121 (108,147) | |

**Notes**: MET denotes metabolic equivalents. Data are median (interquartile range). * Denotes statistical significance at the 5% level.

getting ready.

### 5.5.3 Glycaemic control

#### 5.5.3.1 Day and night

Overall mean sensor glucose was much higher during free-living compared with the controlled study (7.7 mmol/l versus 6.0 mmol/l; $p = 0.028$), with a trend towards increased proportion of time spent in hyperglycaemia (28% versus 17%; $p = 0.059$). The outcomes are summarised in Table 5.3.

The median glucose profile shown in Figure 5.3 was generally higher during free-living, with glucose levels remaining above target range between 20:00 and 23:00. The interquartile range, illustrating glycaemic variability, was also much wider during free-living. This disparity was particularly evident in the evening from 19:00, which is generally the period following consumption of the evening meal. Additionally, women were least active during this time at home, compared with the controlled study where women undertook a 20-minute walk after their evening meal (Figure 5.2).

During the controlled study, glucose levels remained within target range for most of the day, except after breakfast when there was a steep rise in glucose levels. In comparison, during free-living, hyperglycaemia after breakfast was less marked and similar to that observed after the evening meal.

#### 5.5.3.2 Overnight

Overnight mean sensor glucose was 7.5 mmol/l during free-living compared with 5.2 mmol/l during the controlled study; $p = 0.047$ (Table 5.3). Women also had a significantly higher mean glucose at the start of the overnight period (23:00); 9.6 mmol/l versus 5.9 mmol/l, $p = 0.013$.

During the controlled diet and exercise study, zero time was spent in hyperglycaemia overnight compared with 19% at home ($p = 0.028$). The standard deviation of glucose, representing glucose variability, was almost halved; 0.7 mmol/l versus 1.3 mmol/l, $p = 0.022$. This is illustrated in Figure 5.3 by the narrower interquartile range overnight during the controlled study.

Figure 5.2: Physical activity energy expenditure during free-living and controlled study

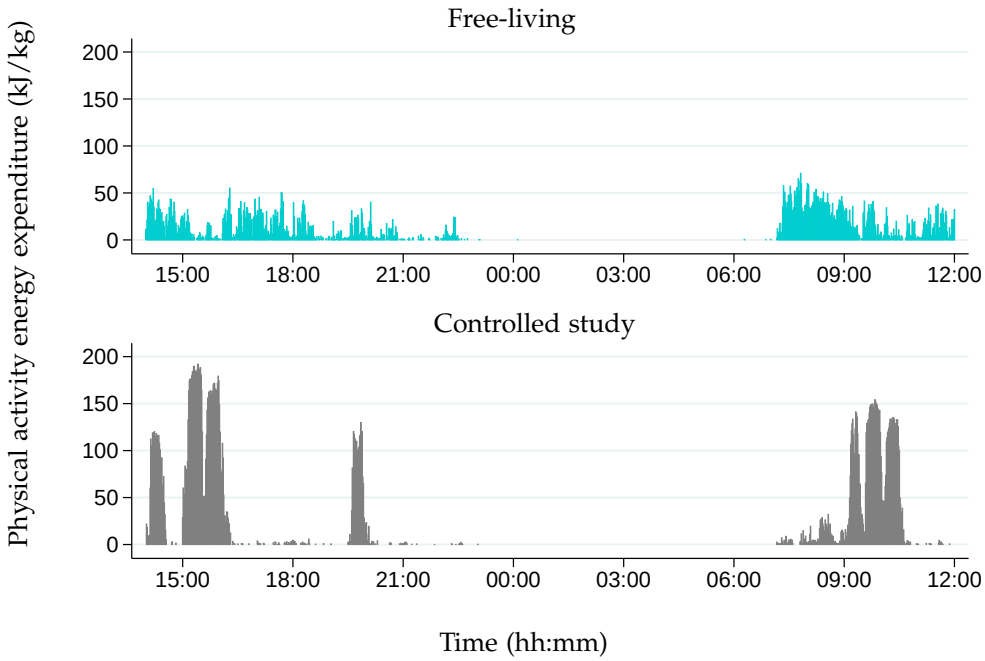



Figure 5.3: Sensor glucose profiles during free-living and controlled study

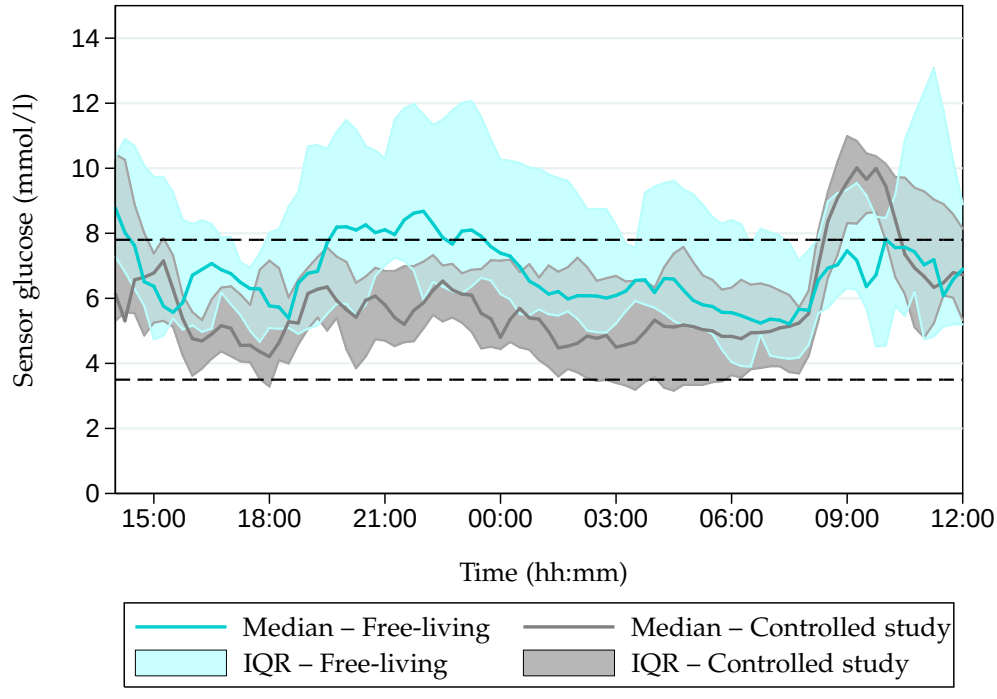


Table 5.3: Sensor glucose outcomes during free-living and controlled study, for 'day and night' and overnight periods

| | Day and night (14:00-12:30) | | | Overnight (23:00-07:30) | | |
|---|---|---|---|---|---|---|
| Outcome | Free-living | Controlled study | P-value | Free-living | Controlled study | P-value |
| Mean sensor glucose (mmol/l) | $7.7 \pm 2.5$ | $6.0 \pm 0.6$ | 0.028* | $7.5 \pm 3.1$ | $5.2 \pm 1.5$ | 0.047* |
| Starting sensor glucose (mmol/l) | $8.6 \pm 1.9$ | $7.7 \pm 3.0$ | 0.241 | $9.6 \pm 4.6$ | $5.9 \pm 1.1$ | 0.013* |
| Standard deviation of sensor glucose (mmol/l) | 2.1 (1.7, 2.9) | 1.7 (1.4, 2.3) | 0.386 | 1.3 (1.0, 1.8) | 0.7 (0.5, 1.1) | 0.022* |
| $3.5 <$ Sensor glucose $\leq 7.8$ mmol/l (%) | 69 (44, 82) | 81 (59, 86) | 0.285 | 75 (42, 87) | 84 (52, 100) | 0.114 |
| Sensor glucose $\leq 3.5$ mmol/l (%) | 2 (0, 6) | 5 (0, 21) | 0.161 | 0 (0, 8) | 0 (0, 34) | 0.176 |
| Sensor glucose $\leq 2.8$ mmol/l (%) | 0 (0, 3) | 0 (0, 4) | 0.500 | 0 (0, 4) | 0 (0, 3) | 0.917 |
| Low blood glucose index | 1.1 (0.5, 3.3) | 2.7 (0.6, 5.4) | 0.139 | 1.2 (0.2, 2.9) | 2.8 (0.3, 9.1) | 0.241 |
| Sensor glucose $> 7.8$ mmol/l (%) | 28 (14, 54) | 17 (10, 22) | 0.059 | 19 (5, 58) | 0 (0, 1) | 0.028* |
| Sensor glucose $> 10.0$ mmol/l (%) | 12 (2, 24) | 4 (1, 6) | 0.074 | 0 (0, 17) | 0 (0, 0) | 0.068 |

**Notes**: Data are mean $\pm$ standard deviation or median (interquartile range). * Denotes statistical significance at the 5% level.

#### 5.5.3.3 Hypoglycaemia

Time spent in hypoglycaemia overall was greater during the controlled study, although not significant (5% versus 2%; $p = 0.161$). There were 17 episodes of hypoglycaemia (1.7 episodes per subject) requiring treatment with 15g rescue carbohydrate. Eleven (65%) episodes occurred during or within two hours of the exercise sessions on the treadmill despite setting of temporary basal infusion rates (70% of women) and consumption of supplementary snacks for exercise according to capillary glucose testing (total amount consumed ranged from 15g to 75g carbohydrate). There was one episode after midnight. Episodes of hypoglycaemia during free-living were not recorded.

## 5.6 Discussion

This is the first study to objectively measure amount and intensity of physical activity energy expenditure in pregnant women with type 1 diabetes. Most of the women studied were in their second trimester of pregnancy. Seven were nulliparous and hence likely to have very different activity patterns from those women with children. The majority of time was spent sedentary (lying down or sitting) or in light intensity activity (e.g. standing, slow walking).[261] Interestingly, the highest PAEE was recorded between 07:30 and 09:00 (Figure 5.2), when women tend to be engaged in domestic tasks such as getting ready, preparing meals for the family and travelling to school or work, suggesting that such habitual light activity accounts for a not insignificant proportion of daily energy expenditure. The lowest PAEE during waking hours was measured from 20:00 to 23:00.

Less than 2% of time (27 minutes) was spent in moderate intensity activity, which is just below the American College of Obstetricians and Gynaecologists recommendation of 30 minutes per day. A study in non-diabetic overweight women in England showed, of the total 742 minutes ambulatory, 585 minutes was spent sedentary, 122 minutes in light activity and 33 minutes in moderate to vigorous activity.[252] Other studies in healthy pregnancy reported times of 57 minutes (Switzerland) and 63 minutes (Sweden) spent at moderate or vigorous intensity.[244; 253] These and other studies assessed energy expenditure in healthy or overweight pregnant women [242; 245; 262], but there is no such data in pregnant women with diabetes.

Although there have been several studies using CGM to assess glycaemic control during pregnancy associated with type 1 and 2 diabetes [215; 223; 258; 259], this

is the first evaluation of a cohort of women exclusively on insulin pump therapy and the first to consider the influence of physical activity. Average glucose was 7.7 mmol/l during free-living, which is above National Institute for Health and Clinical Excellence recommended targets during pregnancy.[94] This level is even higher than a previously observed second trimester glucose of 7.1 mmol/l in a mixed cohort of women with MDI and CSII-treated type 1 and 2 diabetes.[223]

Women spent almost one-third of time hyperglycaemic, similar to that reported earlier,[223] despite almost achieving the recommended 30 minutes of moderate activity daily. This suggests that current exercise guidelines may not be sufficient to achieve glucose targets in pregnancy. Of note, this cohort of women were all optimised on CSII with well controlled diabetes (HbA1c 6.4%) on entering the study. Moreover, they had access to real-time CGM in addition to conventional fingerprick glucose monitoring at home to make adjustments to their insulin regimen and diet. This suggests that the availability of technology is not the sole determinant of improved glycaemic control. This may have been because women were not wearing the device specifically to optimise glucose control and/or because of the challenges in matching insulin to glucose levels in real life. Another reason may have been inexperience in using a new device.

During the 24-hour period including a controlled diet and structured exercise, glucose levels were significantly improved. These benefits were even more striking during the overnight period, with zero time spent in both hypoglycaemia and hyperglycaemia. Glycaemic variability was also reduced, which is clinically significant as fluctuating glucose levels are correlated with an increased risk of severe hypoglycaemia.[177]

Women attained a higher total PAEE with a greater proportion of time spent in moderate intensity activity (121 minutes), during the controlled study. This was achieved without any discomfort, as indicated by the Borg rating of perceived exertion during exercise. Nonetheless, exercise did result in 11 episodes of symptomatic hypoglycaemia within two hours of treadmill sessions. These events occurred despite setting of temporary basal rate reductions and consumption of supplemental carbohydrates prior to and during exercise. There was only one episode after midnight, occurring in a subject who had already experienced four episodes of hypoglycaemia following moderate intensity exercise the afternoon and evening prior. Notably, mean sensor glucose was 5.2 mmol/l at 23:00 during the controlled study. Blood glucose levels below 6 mmol/l at bedtime have been shown to be associated with an increased risk of nocturnal hypoglycaemia in pregnancy.[229]

The treadmill exercise sessions were of moderate intensity, which is associated with a higher risk of decline in glucose levels.[187] Continuous or intermittent higher intensity exercise is less likely to result in hypoglycaemia, although this type of exercise may not be practical in pregnancy.[190] Only one other study to date has evaluated the effect of exercise in pregnant women with type 1 diabetes, showing improved lipid profiles but no benefit on glucose control of a postprandial walking programme.[251]

The controlled diet consisted of nutritionally balanced ($40-50\%$ carbohydrate, $20-30\%$ fat, 20% protein), $50-60$g carbohydrate meals and supplementary snacks for exercise. A study in overweight women with gestational diabetes found that one-hour postprandial capillary glucose was $< 7.8$ mmol/l when meals with $45-55\%$ carbohydrate content were consumed, compared with glucose $< 6.7$ mmol/l following lower carbohydrate ($33-45\%$) meals.[263] In comparison, in my study mean glucose was 6.0 mmol/l during controlled conditions suggesting that glucose targets may be attainable with a moderate dietary intake, without the need for excessive carbohydrate restriction. Although women did not have access to CGM readings, it is likely that they were more engaged in their diabetes and also had more time to fine tune their insulin boluses and basal rates during the 24-hour stay in the clinical research facility.

Compared with free-living, glucose levels were higher after breakfast in the morning under controlled diet and exercise conditions. This period of the day is often the most challenging for women during pregnancy. One possible reason is that women were given a higher carbohydrate breakfast compared to that which may be normally consumed at home. Additionally, during free-living this period was associated with higher activity levels corresponding to when women are actively engaged in household tasks and getting ready for work, in contrast to the controlled study when women were inevitably sedentary in between scheduled walks and exercise.

Light intensity activity alone has been shown to have a positive effect on glycaemic control. An Australian study in overweight men and women at risk of diabetes found a significant association between light intensity physical activity and two hour (post oral glucose tolerance test) plasma glucose, with no such association for moderate or vigorous activity.[264] In my study, reasonable levels of PAEE were achieved during the low intensity walks after meals (Figure 5.2), suggesting even gentle walking may have a benefit on glucose levels.

One of the major strengths of this study was the use of an objective method of quantifying PAEE, compared with subjective measures which may be biased and

prone to overestimation of activity levels.[237] Various methods, including self-report questionnaires, pedometers, heart rate monitors and accelerometers, have been employed in studies evaluating activity levels.[237; 238] The device used in this study was a combined heart rate and movement sensor, which provides a more accurate estimate of PAEE compared with heart rate or accelerometry alone.[221] The device was individually calibrated on each study visit, which reduced the inter-individual variation in measurement. This is particularly relevant in pregnancy due to the physiological effects on heart rate with advancing gestation. Importantly, compliance with wear was 100%, thus improving the reliability of the results. However, the validity of using accelerometry to measure PAEE in pregnancy is undetermined, as it has only been validated in non-pregnant populations. In addition, accelerometers are less sensitive to detecting the lower intensity activity levels common in pregnancy [242]. The Actiheart device has been used in two recent studies in healthy pregnant women in Sweden and Switzerland.[244; 245]

The free-living observations in this study provide reference data which may be clinically useful. Elevated glucose levels in the evening before going to bed corresponded to the least active period of the day, whilst glucose levels remained in target in the morning when women were most active. These results suggest a benefit of physical activity on glycaemic control, and may help in the development of recommendations on timing and intensity of physical activity during diabetic pregnancy.

Limitations of my study include the small number of subjects studied, and the evaluation of a single day which may not be representative of usual glycaemic control. All of the women were of Caucasian ethnicity, in full or part-time employment, and living with a partner. These demographic characteristics may influence activity levels and degree of self-efficacy in diabetes management, and hence limit generalisability of the results to all women with type 1 diabetes during pregnancy. Fitness levels of the participants may have also had an influence on glycaemic responses observed during exercise. Women who volunteer to take part in research are generally more motivated and engaged in their diabetes care, which may also include a higher likelihood of undertaking regular exercise. In addition, the active monitoring of glucose and activity levels during the free-living period of the study may have motivated women to exercise more and be more vigilant in managing their diabetes.

The controlled study was not designed specifically to evaluate the effect of exercise on glycaemic control. Hence, it was not possible to differentiate between the influence of diet, insulin and physical activity on glucose levels. Similarly, during free-living women consumed meals and snacks ad libitum and a diet record was not

obtained.

## 5.7 Conclusions

This study describes the first objective data on activity patterns and energy expenditure in combination with glucose levels in pregnant women with type 1 diabetes during free-living. Despite having well-controlled diabetes treated by insulin pump therapy and almost achieving the daily exercise goals for pregnancy, glucose levels were above recommended targets, with almost a third of the day spent hyperglycaemic. As a much higher proportion of time was spent sedentary or in light activity, guidelines incorporating daily targets for light intensity exercise may be more appropriate and achievable in the setting of pregnancy.

This data may serve as a reference for clinicians when titrating daytime basal insulin regimens to optimise glycaemic control whilst minimising the risk of hypoglycaemia during pregnancy. In addition, this information may be used to aid in the refinement and tailoring of algorithms used to drive insulin delivery in a future artificial pancreas system.

A programme of structured low and moderate intensity exercise with a controlled diet resulted in improved glucose levels. Exercise may be crucial to achieving near-normal glucose control, but even in a controlled setting hypoglycaemia could not be prevented.

# Chapter 6

# Sensor accuracy during exercise in pregnancy

## 6.1 Background

### 6.1.1 Utility of CGM in exercise

Exercise in type 1 diabetes is associated with a significantly increased risk of hypoglycaemia.[187] Despite awareness of the benefits of exercise, the fear of hypoglycaemia often results in over-compensatory behaviours such as excess carbohydrate consumption or avoidance of exercise, which are associated with worse metabolic control.[126] Guidelines for type 1 diabetes recommend checking capillary glucose at least twice before and every 30 minutes during exercise as well on recovery.[226] This regimen can be difficult to adhere to, particularly if activity must be interrupted to carry out fingerprick testing. In addition, the information obtained is limited to isolated glucose measurements. A survey of endurance athletes with type 1 diabetes found that although the majority monitored glucose levels before and after exercise, only 50% reported checking during exercise.[265]

The emergence of CGM over the last decade has provided both patients and clinicians with a much more detailed picture of glycaemic control.[9] This is especially useful during physical activity where CGM may serve as a tool to recognise impending hypoglycaemia or hyperglycaemia, thus enabling appropriate modifications in therapy. Additionally, CGM may play an important role in detecting delayed, including nocturnal, hypoglycaemia that may otherwise go unnoticed when exercise is performed later in the day.[194]

CGM may increase self efficacy during sport by providing glucose readings in real-time without the need to discontinue exercise, and empower patients to make more informed decisions regarding insulin and carbohydrates prior to and during physical activity. Real-time CGM in patients with type 2 diabetes has been shown to have a positive effect on modification of dietary and exercise habits, evidenced by improvement in body mass index and HbA1c levels.[266]

CGM may be favoured over fingerprick testing for certain activities, such as during sporting competitions when such checks are not practical. The utility and accuracy of CGMS Gold (Medtronic, Northridge, CA, USA) in detecting hypoglycaemia during scuba diving, when symptoms of hypoglycaemia may not be easily recognised, has been demonstrated.[267]

### 6.1.2 CGM performance during exercise

Optimal performance of currently available CGM devices is limited by calibration errors and a physiological time lag of glucose transport between blood and interstitial fluid compartments, as well as a device-dependent delay associated with sensor signal processing and filtering out measurement noise. Accuracy, as measured by the median relative absolute difference (RAD) between paired sensor and reference glucose values, ranges from 11% to 14% under resting conditions.[17; 21] Performance may be lower at the extremes of the glucose range or when levels are changing rapidly, both situations of which are commonly associated with exercise.

There are a limited number of studies to date evaluating CGM during physical activity. Accuracy of the Guardian REAL-Time CGM (Medtronic, Northridge, CA, USA) was lower during moderate intensity exercise, with mean RAD ranging from $22-28\%$ and consistent sensor under-reading during hyperglycaemia.[207; 268] The previous generation CGMS Gold (Medtronic, Northridge, CA, USA) was evaluated in 58 adolescents during three separate sports camps, showing a mean RAD of 23% overall, with 43% in the hypoglycaemic ($<$ 3.9 mmol/l) and 18% in the hyperglycaemic range ($>$ 10 mmol/l).[269] Evaluation of the FreeStyle Navigator CGM (Abbott Diabetes Care, Alameda, CA, USA) in 30 children with type 1 diabetes demonstrated a median RAD of 17% during 60 minutes of treadmill exercise improving to 11% with incorporation of a 10-minute sensor lag, compared with a median RAD of 12% over the 24-hour study period.[270]

Current CGM devices employ a glucose oxidase-based sensor which is sensitive to changes in pH. Theoretically, a fall in pH during intense anaerobic exercise due

to the generation of lactic acid may affect sensor accuracy. This was examined in a study in healthy males, showing no variation in CGMS Gold (Medtronic, Northridge, CA, USA) readings with physiological changes in pH provoked by a short period of intense activity.[271]

Errors in calibrating CGM may be related to inherent imprecision in the blood glucose meter used and/or the timing of calibrations.[21] Accuracy may be improved by avoiding device calibration when glucose levels are changing rapidly such as occurs during exercise, due to the disequilibrium between interstitial and blood glucose concentrations. Accuracy of CGMS Gold (Medtronic, Northridge, CA, USA) was assessed in 50 adolescents with type 1 diabetes, reporting a median RAD of 13% when rate of change of glucose was $< 0.03$ mmol/l/min, and 19% when $\geq 0.08$ mmol/l/min.[44] Additional calibrations resulted in only a modest improvement in overall sensor accuracy and a 4% increase in detection of episodes of exercise-induced hypoglycaemia. In contrast, overnight accuracy was better when daytime calibrations were removed.

The physiological delay in glucose transport is further exaggerated at extreme and/or rapidly changing glucose levels. A lag time of up to 20 minutes in the detection of falling glucose levels was observed with the Guardian REAL-Time (Medtronic, Northridge, CA, USA) during moderate intensity exercise.[272] This compares with a lag time of $8 - 12$ minutes for the next generation Enlite sensor (Medtronic, Northridge, CA, USA) at rest.[18] Such transport delays, in addition to glucose measurements being limited to every one to five minutes depending on the CGM device used, may result in underestimation of a decline in blood glucose with exercise.

Device size, including the need to carry an external transmitter, may be a drawback for some patients, particularly during contact or water sports. Additionally, problems with adhesiveness may be exacerbated during exercise as a result of perspiration.[41] The non-invasive GlucoWatch Biographer (Cygnus, Redwood City, CA, USA), which is no longer available for clinical use, was the first CGM device to be tested during exercise, demonstrating a progressive decline in accuracy with more intense activity and a high skip rate predominantly due to perspiration.[273] In a field study of adolescents during three sports camps, one third of CGMS Gold (Medtronic, Northridge, CA, USA) sensors required replacing within 48 hours, as a result of disconnection due to tape problems from sweating or loss of signal.[269] Accuracy was lower for high-contact activities, as observed by a mean RAD of 19%, 24% and 27% for the golf, soccer, and floorball with cross-country skiing camps, respectively. The GlucoDay (Menarini Diagnostics, Florence, Italy) was worn during exercise of

varying intensity on a cycle ergometer, showing 99.3% of values in zones A and B of the Clarke error grid analysis.[274] However, 39% of the inserted microfibre sensor probes broke during exercise due to the mechanical stress exerted by exercising muscles, limiting use of the device during physical activity.

### 6.1.3 CGM in pregnancy

Although there have been several studies reporting on the accuracy of CGM outside of pregnancy, there is minimal evidence regarding its performance in the pregnant state where shifts in interstitial fluid may have an influence.[255] CGMS Gold (Medtronic, Northridge, CA, USA) was evaluated in 15 pregnant women with type 1 diabetes, using capillary fingerprick testing as reference glucose. The mean absolute difference between paired sensor and reference glucose values was 0.74 mmol/l, with 93.8% of values in zones A and B of the Clarke error grid analysis.[275] In a more recent study, performance of the FreeStyle Navigator (Abbott Diabetes Care, Alameda, CA, USA) was evaluated during overnight closed-loop insulin delivery in ten women with type 1 diabetes.[108] Using plasma glucose as reference, the median RAD was 11.4%, with 94.6% of glucose readings in the safe zones of the Clarke error grid analysis.

## 6.2 Rationale

The majority of studies evaluating efficacy of CGM have been performed under sedentary conditions. Only a few studies have been carried out during exercise, all of which employed the older generation sensors which are no longer available or have been superseded by newer generation devices. There are no studies objectively assessing accuracy during physical activity using currently available CGM devices, in particular none during pregnancy.

## 6.3 Aim

The aim of this study was to evaluate performance of a current generation CGM during moderate intensity exercise, in pregnant women with type 1 diabetes.

## 6.4 Methods

### 6.4.1 Study design

As part of a study evaluating closed-loop insulin delivery in pregnant women with CSII-treated type 1 diabetes during normal daily activities, performance and accuracy of CGM during moderate intensity exercise was measured. The full protocol is described in Chapter 4. The study protocol was approved by the local Research Ethics Committee and all participants gave written informed consent.

Twelve women attended a clinical research facility for two 24-hour visits (closed-loop and conventional CSII), from midday until 12:30 the following day. Subjects undertook two 55-minute sessions of moderate intensity exercise: in the afternoon (15:00-16:00) on day one and morning (09:30-10:30) on day two. Each session involved two 25-minute periods of brisk walking at speeds ranging from $2.6 - 4.8$ km/h on a treadmill, with a 5-minute rest interval.

### 6.4.2 Measurements

#### 6.4.2.1 Continuous glucose monitoring

The FreeStyle Navigator CGM (Abbott Diabetes Care, Alameda, CA, USA) with a one hour run-in calibration period was used to measure sensor glucose (Figure 1.1). The sensor was inserted one to two days prior to each study visit, and worn for the duration. The sensor was placed in either the abdomen or upper arm according to preference, and calibrated with capillary glucose measurements as per manufacturers' instructions.

#### 6.4.2.2 Reference glucose

Blood sampling for reference glucose was carried out at $15 - 30$ minute intervals throughout study visits, via a peripheral intravenous cannula inserted on arrival. Plasma glucose was measured in real-time on a YSI 2300 STAT Plus analyser (YSI Ltd, Fleet, UK). During each exercise session, blood samples were taken prior to, at halfway, and at the end of exercise, and at 30-minute intervals during the two-hour recovery period.

### 6.4.3 Statistical analysis

Analyses were conducted using IBM SPSS Version 17 (SPSS Inc, Chicago, IL, USA), GStat software Version 1.1.2 (University of Cambridge, Cambridge, UK) and Stata Version 11 (StataCorp LP, Texas, USA). Level of statistical significance was set at $p < 0.05$. Plasma glucose was used as reference glucose. Each sensor value was paired with the nearest plasma glucose within $\pm 1$ minute. Difference (bias) and relative absolute difference (RAD) were calculated for each pair, measured hourly. Hourly paired sensor-reference glucose values were analysed to reduce the effect of auto-correlated errors. The median relative absolute rate of change of plasma glucose was calculated as the absolute difference between consecutive plasma glucose values divided by the average plasma glucose over that hour. Plasma and sensor glucose levels at the start and end of each exercise session are expressed as mean and standard deviation.

Each pair was evaluated to determine whether the CGM value met the International Organisation for Standardisation (ISO) requirements for blood glucose monitoring systems (percentage of CGM values within $\pm 0.8$ mmol/l when reference blood glucose $\leq$ 4.2 mmol/l, or within $\pm 20\%$ when reference $>$ 4.2 mmol/l).[11] Median bias, RAD and ISO criteria were evaluated for the overall period, as well as for hypoglycaemic ($\leq$ 3.5 mmol/l), target ($3.5 - 7.8$ mmol/) and hyperglycaemic ($>$ 7.8 mmol/l) ranges.

Comparisons were made for three periods:

- **Afternoon exercise (15:00-18:00).** 'Afternoon exercise' evaluated sensor accuracy during moderate intensity exercise from 15:00 to 16:00 and the post-exercise recovery period.
- **Sedentary (18:00-09:00).** 'Sedentary' evaluated sensor accuracy when subjects were resting including the overnight period.
- **Morning exercise (09:00-12:00).** 'Morning exercise' evaluated sensor accuracy during moderate intensity exercise from 09:30 to 10:30 and the post-exercise recovery period.

Differences in RAD, bias, and relative absolute rate of change of plasma glucose between the three conditions were analysed using two-way analyses of variance (ANOVA), adjusting for rate of change of plasma glucose. A rank normal transformation was performed for RAD and rate of change of plasma glucose as the data were

non-normally distributed, thus enabling ANOVA to be performed. Post hoc analyses included Tukey's and Bonferroni's tests. ISO was analysed by logistic regression using the enter method.

The relationship between bias and rate of change of plasma glucose was plotted for all data and assessed using linear regression to derive a correlation coefficient.

All paired sensor and reference glucose values were plotted using the Clarke error grid analysis, and expressed numerically as proportion of values in each of zones A to E.[10]

Bland-Altman plots were used to illustrate the relationship between CGM error and the true glucose values.[276] The difference between sensor and plasma glucose (bias) was plotted against the mean of both, for all paired data. The mean of the differences is indicated by a dashed horizontal line with $\pm 1.96$ standard deviations representing the 95% confidence interval of the difference between the two measurement methods.

## 6.5 Results

### 6.5.1 CGM wear

The FreeStyle Navigator CGM (Abbott Diabetes Care, Alameda, CA, USA) was worn for 24 study visits carried out in the clinical research facility. Sensors were in situ for at least 24 hours prior to each study visit. Nine women wore the sensor on the upper arm and three on the abdomen, for both study visits. Compliance with CGM wear was 100% for the duration of each study visit, and none of the sensors required replacing. There were no occurrences of disconnection of the sensor, even during exercise.

### 6.5.2 CGM accuracy

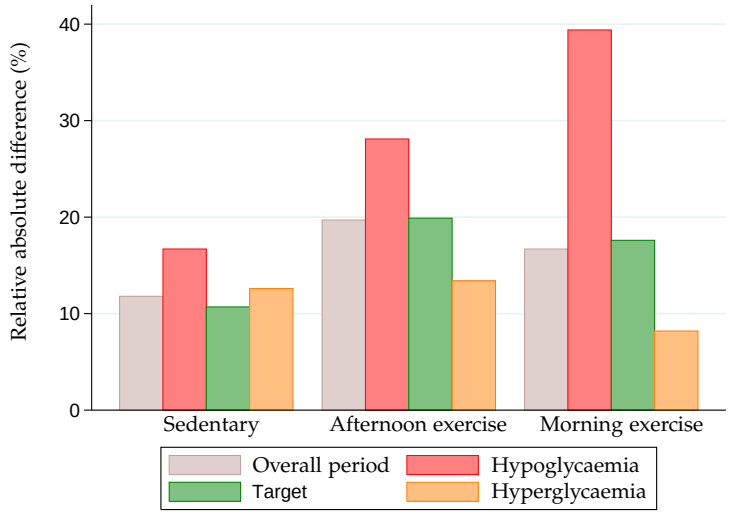
The period analysed spanned from 15:00 on day one until 12:00 on day two (total 21 hours). There were 493 paired sensor and reference glucose values in total used for evaluation: 351 during sedentary periods and 142 during exercise. The results are summarised in Table 6.1.

The overall median RAD between sensor and reference (plasma) glucose was 11.8% under sedentary conditions compared with 19.7% and 16.7% during afternoon and morning exercise, respectively; $p < 0.001$, ANOVA (Figure 6.1). Post hoc analyses revealed a significant difference between exercise and resting conditions

Table 6.1: Summary of sensor accuracy measures during sedentary and exercise periods

| | Sedentary period | | Afternoon exercise | | Morning exercise | | P-value (ANOVA) |
|---|---|---|---|---|---|---|---|
| *Number of data pairs* | | | | | | | |
| Overall | 351 | | 72 | | 70 | | |
| Target | 269 | | 48 | | 29 | | |
| Hypoglycaemia | 23 | | 18 | | 26 | | |
| Hyperglycaemia | 59 | | 6 | | 15 | | |
| *Median bias (mmol/l)* | | | | | | | |
| Overall | 0.16 | | 0.63 | | 0.77 | | $< 0.001$* |
| Target | 0.11 | | 0.66 | | 0.90 | | |
| Hypoglycaemia | 0.54 | | 0.77 | | 0.78 | | |
| Hyperglycaemia | $-0.22$ | | $-0.78$ | | $-0.46$ | | |
| *ISO criteria (%)* | | | | | | | |
| Overall | 76.1 | | 59.0 | | 62.6 | | 0.003* |
| Target | 77.1 | | 58.3 | | 60.2 | | |
| Hypoglycaemia | 70.8 | | 54.8 | | 53.8 | | |
| Hyperglycaemia | 76.2 | | 84.6 | | 90.0 | | |
| *Clarke error grid analysis (%)* | | | | | | | |
| Clinically acceptable | 96 | | 87 | | 86 | | |
| Potentially unsafe | 4 | | 13 | | 14 | | |
| *Relative absolute difference (%)* | Median | IQR | Median | IQR | Median | IQR | |
| Overall | 11.8 | (5.7, 19.5) | 19.7 | (11.5, 34.6) | 16.7 | (9.2, 34.6) | $< 0.001$* |
| Target | 10.7 | (5.4, 18.4) | 19.9 | (11.5, 33.3) | 17.6 | (9.4, 34.5) | |
| Hypoglycaemia | 16.7 | (9.8, 33.4) | 28.1 | (15.9, 41.6) | 39.4 | (18.5, 55.4) | |
| Hyperglycaemia | 12.6 | (3.3, 18.2) | 13.4 | (7.3, 19.4) | 8.2 | (4.7, 14.9) | |
| | Median | IQR | Median | IQR | Median | IQR | |
| Plasma glucose relative absolute rate of change (%/hour) | 11.9 | (5.5, 22.7) | 20.3 | (9.9, 38.9) | 22.4 | (11.3, 39.0) | $< 0.001$* |

Figure 6.1: Median relative absolute difference between sensor and plasma glucose pairs for sedentary and exercise periods, by glucose range




($p < 0.001$), with no difference for afternoon versus morning exercise ($p = 0.900$). Combining the two exercise periods, overall median RAD was 18.7% compared with 11.8% under sedentary conditions ($p < 0.037$, ANOVA).

Analysis by glucose range demonstrated largest RAD in hypoglycaemia, during sedentary (16.7%) and both exercise conditions, particularly during morning exercise (39.4%) (Table 6.1). Sensor accuracy was superior during sedentary period for all glucose ranges compared with afternoon and morning exercise, as shown by the lower median RAD in Figure 6.1.

Under resting conditions, 76.1% of CGM values met ISO criteria, compared with 59.0% during afternoon and 62.6% during morning exercise; $p = 0.003$ (Table 6.1).

CGM over-estimated plasma glucose, as measured by median bias, by 0.16 mmol/l during resting conditions, compared with 0.63 mmol/l and 0.77 mmol/l during afternoon and morning exercise overall, respectively ($p < 0.001$, ANOVA) (Table 6.1). Post hoc analyses revealed a significant difference between exercise versus resting conditions ($p < 0.001$), with no difference between afternoon and morning exercise ($p = 0.390$). During sedentary conditions, the greatest bias was seen in the hypoglycaemic range (+0.54 mmol/l).

The Bland-Altman plots illustrate the observed bias over the range of glucose

concentrations (Figure 6.2). Under sedentary conditions, the majority of values were within the 95% confidence interval. Values outside these limits were evenly distributed across the range of glucose concentrations, with a tendency for CGM overestimation during hyperglycaemia and underestimation during hypoglycaemia (panel 6.2a).

During afternoon exercise there was a greater proportion of outlying values in the negative bias range, indicating sensor underestimation (panel 6.2b). During morning exercise there was similar over- and under-reading by the sensor across the glucose range with only a few values outside the 95% confidence interval (panel 6.2c).

Using the Clarke error grid analysis, 96% of values were in the clinically acceptable zones A + B during resting conditions, compared with 87% during afternoon exercise and 86% during morning exercise (Table 6.1). Figure 6.3 displays the plotted paired sensor and plasma glucose measurements. Zone D contained 4% of points during rest and $13-14$% during exercise. There were no values in zones C or E.

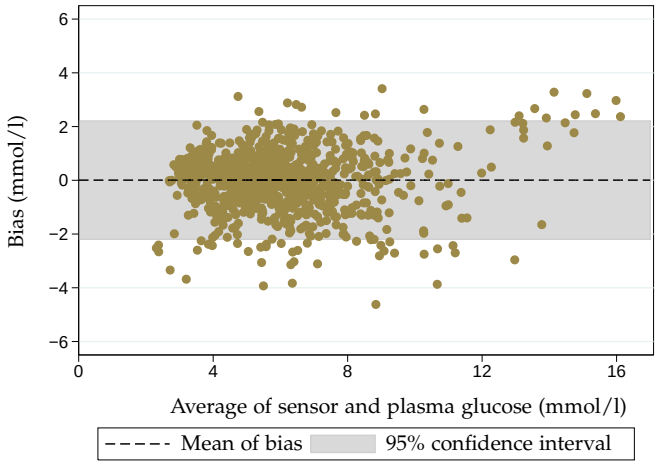
### 6.5.3 Rate of change of glucose

The relative absolute rate of change of plasma glucose was significantly lower during sedentary (11.9%) conditions compared with afternoon (20.3%) and morning exercise (22.4%); $p < 0.001$, ANOVA. Even after adjusting for the relative absolute rate of plasma glucose change, the differences in median RAD between resting and the two exercise periods remained significant ($p < 0.001$). When the sedentary period was excluded from the analysis, there was no difference between the two exercise periods after adjusting for the relative absolute rate of plasma glucose change ($p = 0.568$).

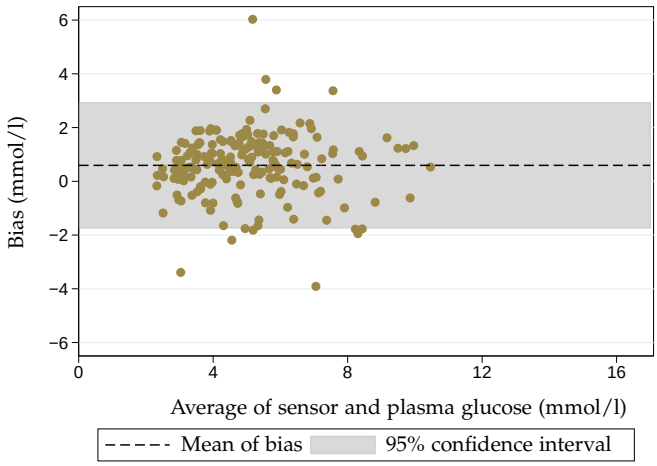
The plasma and sensor glucose profiles during afternoon and morning exercise sessions are shown in Figure 6.4. Plasma glucose declined by $1.2 \pm 1.8$ mmol/l, compared with $0.9 \pm 1.6$ mmol/l for sensor glucose ($p = 0.255$), from start to end of afternoon exercise. There was a significant difference between mean plasma and CGM glucose at the end of afternoon exercise ($4.8 \pm 1.6$ mmol/l versus $5.5 \pm 1.7$ mmol/l; $p = 0.036$). Similarly, at the end of morning exercise, plasma glucose was $5.9 \pm 3.1$ mmol/l and CGM was $7.3 \pm 2.5$ mmol/l ($p < 0.001$), with a more rapid decline in plasma glucose ($2.9 \pm 2.6$ versus $2.1 \pm 2.5$; $p = 0.003$). Of note, exercise was commenced at higher plasma glucose in the morning ($8.8 \pm 2.6$ mmol/l) compared with $6.0 \pm 1.8$ mmol/l prior to afternoon exercise. These results indicate sensor over-reading as plasma glucose levels were falling with exercise. Mean fingerprick capillary glucose readings performed before, during and after exercise were gener-

Figure 6.2: Bland Altman plots during sedentary and exercise periods

(a) Sedentary period




(b) Afternoon exercise




(c) Morning exercise

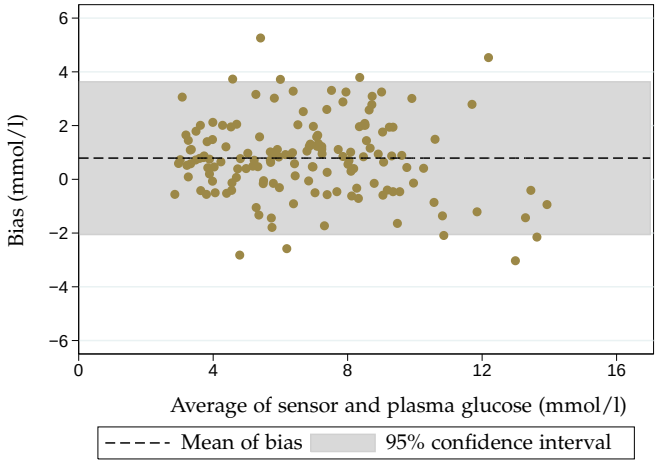
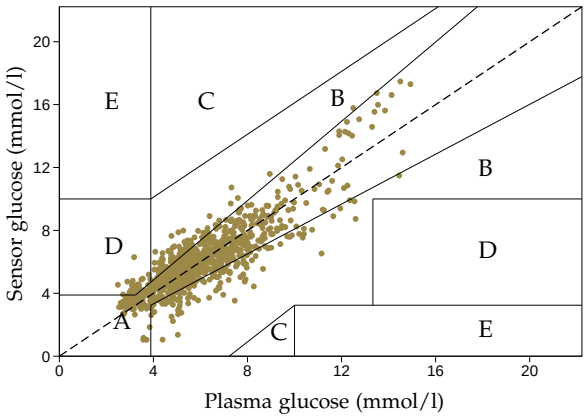


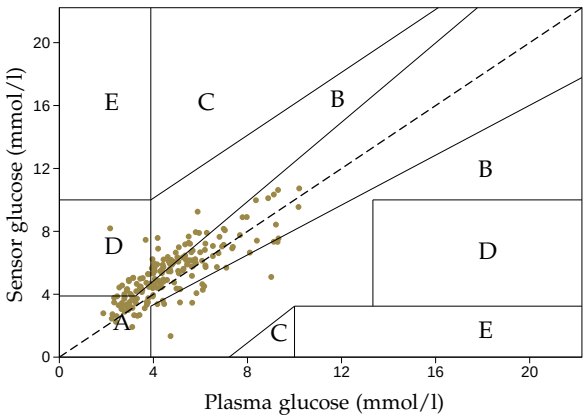
Figure 6.3: Clarke error grid analysis during sedentary and exercise periods

(a) Sedentary conditions



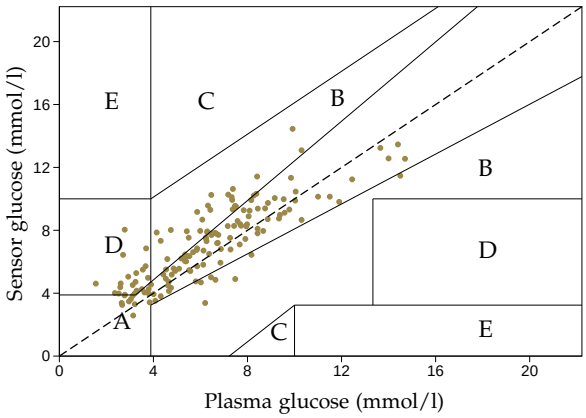

| Zone | Frequency (%) |
|---|---|
| A | 76 |
| B | 20 |
| C | 0 |
| D | 4 |
| E | 0 |

(b) Afternoon exercise




| Zone | Frequency (%) |
|---|---|
| A | 61 |
| B | 26 |
| C | 0 |
| D | 13 |
| E | 0 |

(c) Morning exercise




| Zone | Frequency (%) |
|---|---|
| A | 61 |
| B | 25 |
| C | 0 |
| D | 14 |
| E | 0 |

ally higher than concurrent plasma glucose values (Figure 6.4). These discrepancies were not significant for end of afternoon (capillary glucose $5.6 \pm 1.0$ mmol/l versus plasma glucose $4.8 \pm 1.6$ mmol/l; $p = 0.219$) or morning exercise (capillary glucose $6.7 \pm 2.7$ mmol/l versus plasma glucose $5.9 \pm 3.1$ mmol/l; $p = 0.084$).

Figure 6.5 illustrates the negative relationship between sensor bias and rate of change of plasma glucose, indicating negative bias (sensor under-reading) with increasing plasma glucose, and positive bias (sensor over-reading with declining glucose. The correlation coefficient (R) was significant for both sedentary conditions ($R = 0.548$; $p < 0.001$), and afternoon ($R = 0.775$; $p < 0.001$) and morning ($R = 0.590$; $p < 0.001$) exercise. The strongest correlation was demonstrated during afternoon exercise.

## 6.6 Discussion

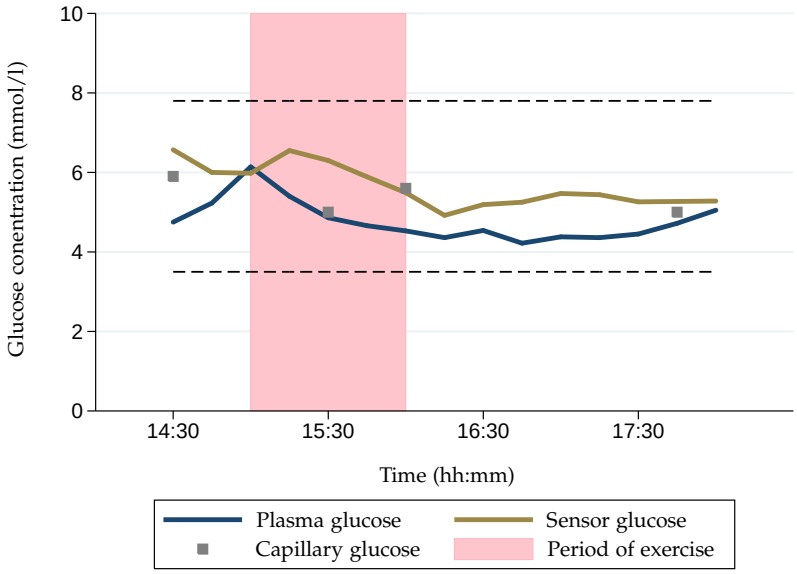
This is the first evaluation of accuracy of CGM during physical activity in pregnancy. Only one other study assessed sensor performance in pregnancy using plasma glucose as reference, as part of a feasibility study of closed-loop insulin delivery.[108] In that study, median RAD was 11.4% under sedentary conditions, which is comparable with the median RAD of 11.8% observed in my study during the sedentary period. Another study of CGM during pregnancy used capillary glucose as the reference and did not involve exercise.[275] The median RAD observed at rest in my study is comparable to values measured in non pregnant populations ($11 - 14\%$),[17; 21] suggesting that CGM performance is not compromised by pregnancy itself.

The higher median RAD during exercise suggests inferior performance of CGM during physical activity. Similar results have been reported in children (median RAD 17%) [269; 270] and non-pregnant adults (mean RAD $23 - 28\%$).[207; 268] In my study, 13% of values during exercise were in the potentially unsafe zones of the Clarke error grid analysis, compared with only 4% at rest. All of these values were in zone D, indicating that most of the inaccuracy could be attributed to lack of sensor responsiveness to rapid changes in glucose concentration. There were no values in zone C or E, associated with overcorrection or erroneous CGM behaviour, respectively.

The minimum acceptable ISO system accuracy requirements for SMBG require that at least 95% of individual glucose results meet the stipulated criteria for blood glucose monitoring systems (ISO 15197:2003).[11] In Europe, self monitoring blood glucose devices must comply with this standard prior to obtaining the *Conformité Européenne* label by the regulatory authority. In a study comparing 27 capillary glucose

Figure 6.4: Plasma and sensor glucose profiles during afternoon and morning exercise and recovery periods

(a) Afternoon exercise




(b) Morning exercise

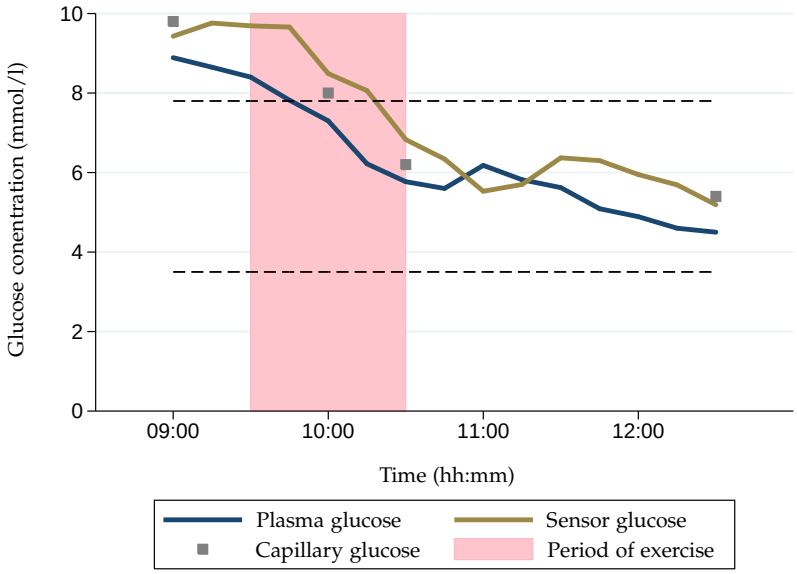
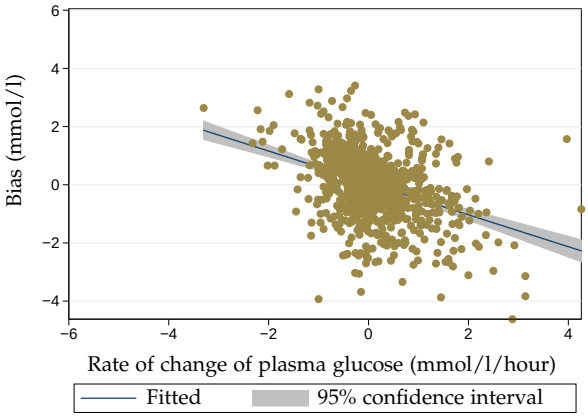


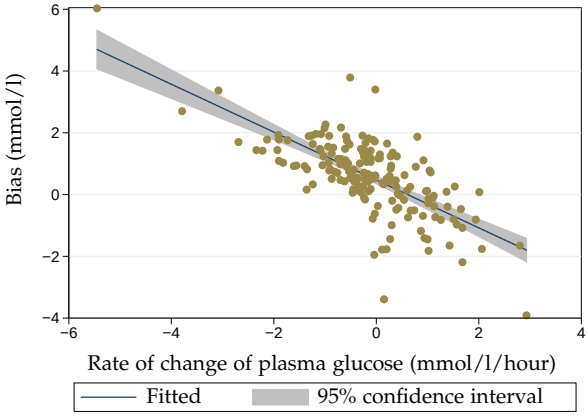
Figure 6.5: Relationship between sensor bias and rate of change of plasma glucose

(a) Sedentary conditions



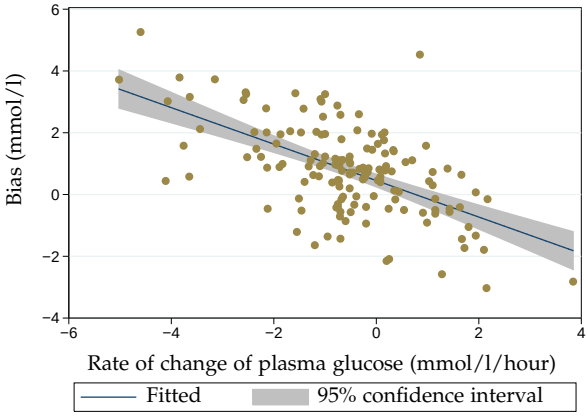

**Fitted model**:
$y = 0.063 - \underbrace{0.548}_{p < 0.001} x$
$R^2 = 0.14$
$n = 905$

(b) Afternoon exercise




**Fitted model**:
$y = 0.473 - \underbrace{0.775}_{p < 0.001} x$
$R^2 = 0.49$
$n = 184$

(c) Morning exercise




**Fitted model**:
$y = 0.452 - \underbrace{0.590}_{p < 0.001} x$
$R^2 = 0.35$
$n = 149$

**Notes**: $y$ = Bias and $x$ = Rate of change of plasma glucose.

monitoring devices, 95% of glucose values for each device met the ISO standard.[8] Similarly, between 90% and 99% of values of five commercially used home blood glucose monitoring devices were within acceptable range.[277] The ISO criteria may also by applied to CGM devices. In my study, only 76% of FreeStyle Navigator CGM values met the ISO standard during sedentary conditions, with an even lower proportion under exercise conditions.

At the end of the exercise sessions, plasma glucose levels were lower than CGM (4.8 mmol/l versus 5.5 mmol/l for afternoon, and 5.9 mmol/l versus 7.3 mmol/l for morning exercise), suggesting a delay in the response of CGM to declining glucose levels, most likely due to the delay in transport of glucose from blood to the interstitial compartment. This observation is clinically significant as inaccurate estimation of glucose control based on CGM values whilst exercising may lead to failure to recognise and treat true hypoglycaemia. CGM under-reading in the hyperglycaemic range has been observed previously.[207] Incorporation of a lag time between interstitial and plasma glucose, which may be increased during exercise, may improve accuracy.[270]

Fingerprick glucose readings taken during exercise tended to be higher than corresponding plasma glucose (Figure 6.4). This is another important clinical observation as the majority of patients currently rely on conventional capillary glucose monitoring during exercise.

Inferior performance of CGM during physical activity may be correlated with the rapid fluxes in glucose levels associated with exercise. In my study, however, sensor accuracy appeared to be higher in the morning (RAD 16.7%) when plasma glucose was changing more rapidly (22.4% rate of change), compared with afternoon exercise (RAD 19.7%) when rate of change of glucose was 20.3%.

There was a significant negative correlation between bias and rate of change of plasma glucose during both sedentary and exercise conditions, with the greatest correlation during afternoon exercise. When rate of change of plasma glucose was included as a covariate in the ANOVA model, there was still a significant difference in accuracy as measured by median RAD between resting and exercise periods, suggesting that rate of change alone does not account for the observed differences in accuracy.

The majority of studies evaluating accuracy of CGM have been carried out under sedentary conditions, hence there is a lack of data on the influence of factors related to exercise such as changes in subcutaneous tissue circulation and increased temperature. Rapid shifts in ambient temperature have been shown to result in at

least 5% over or underestimation of glucose results by conventional self-monitoring blood glucose devices.[278] When moving between environments differing in ambient temperature, it is suggested that patients wait at least 15 minutes before testing to allow for temperature equilibration of both the meter and glucose strips. Performance of microdialysis-based CGM devices is influenced by temperature with a 4% variation in current signal observed for each change in degree centigrade.[279] This is thought to be associated with the catalytic activity of glucose oxidase, permeability of the microdialysis probe to glucose and water solubility of oxygen. Application of a temperature-compensating algorithm resulted in improved accuracy of the next generation microdialysis-based sensor, GlucoMenDay (Menarini, Florence, Italy).[15] Changes in temperature may also hinder the performance of newer non-invasive continuous glucose sensors such as those employing infrared or impedance spectroscopy.[22] However, there is no data suggesting an effect of temperature on the more commonly used needle-based CGM devices, as employed in my study.

Decline in pH, as occurs with the development of lactic acidosis during more intense exercise, has not been shown to affect sensor performance.[271] Errors due to variations in oxygen concentration of blood are less likely in the current generation glucose oxidase-based CGM devices. Calibration of the device also has an important effect on accuracy, which may be improved by avoiding calibration at times of rapidly changing glucose or glucose extremes.[21]

Another potential source of inaccuracy is sensor dislodgement due to sweating, or direct mechanical forces on sensors sited in exercising limbs.[269; 273; 274] In my study there were no problems with loss of signal or missed readings during exercise. Sensors remained intact for the duration of the study visit in all participants, although the intensity of exercise performed may not have been high enough to precipitate displacement.

The major strength of this analysis was the use of plasma glucose as reference, allowing objective evaluation of sensor glucose performance. Reference plasma glucose was measured using a YSI 2300 STAT Plus analyser, which is regarded as a gold standard for analysing blood glucose. The CGM was calibrated with capillary glucose according to manufacturers' instructions, which provides a better representation of performance of CGM in the real life setting, unlike previous studies where blood glucose measurements were used to calibrate the CGM device.[269]

Another important strength was the evaluation of a current generation CGM device commercially available in Europe, which enables direct applicability of the results in clinical practice. However, as physical activity has a complex and variable

effect on glucose control, these observations of CGM performance may not be applicable to other intensities, timing or duration of physical activity. Studies evaluating currently available CGM devices under various exercise conditions and in larger numbers of subjects are required.

## 6.7 Conclusion

This is the first objective evaluation of CGM in pregnant women with type 1 diabetes during normal daily activities, demonstrating feasibility of CGM during moderate intensity exercise whilst maintaining reasonable performance. Sensor accuracy was lower when glucose levels were in the hypoglycaemic range during both sedentary and exercise conditions. Although accuracy was reduced during exercise, this difference was only partly explained by the higher rate of change of glucose associated with physical activity. Over 13% of sensor glucose measurements during exercise were considered clinically unsafe. There was a tendency for CGM to lag behind and hence overestimate plasma glucose as levels declined with exercise. These observations can be directly applied to CGM use in clinical practice, and additionally will need to be considered in the future development of closed-loop insulin delivery systems for use during normal daily activities including exercise.

# Chapter 7

# Conclusions

## 7.1 Summary of results

Closed-loop insulin delivery was evaluated in three randomised crossover studies in 24 adults and 12 pregnant women with type 1 diabetes, in a controlled setting. The results are summarised in Figure 7.1.

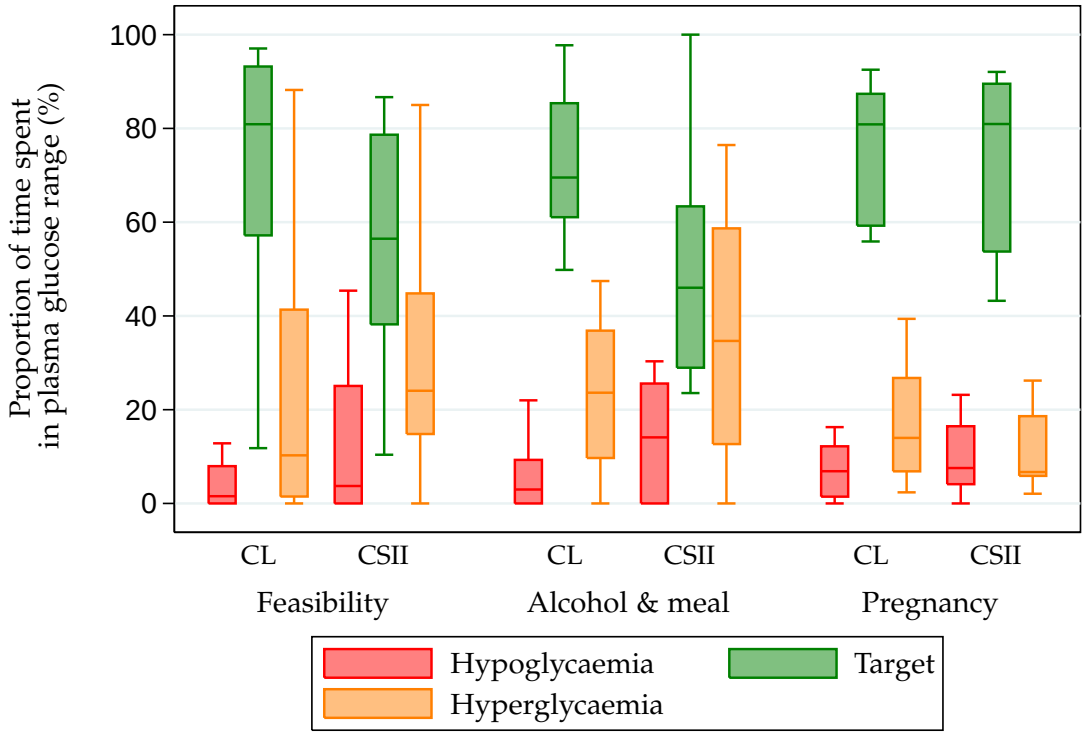
### Feasibility of overnight closed-loop insulin delivery

The feasibility study confirmed the safety and efficacy of overnight closed-loop insulin delivery in adults with type 1 diabetes, following a standard evening meal. Compared with conventional insulin pump therapy (CSII), closed-loop increased the time spent in target glucose ($3.9 - 8.0$ mmol/l) by 24% and reduced glycaemic variability. Importantly, there was a halving of the low blood glucose index measuring duration and extent of hypoglycaemia, and a trend towards less time spent below 3.9 mmol/l during closed-loop. The benefits were proportional to time spent using closed-loop, as indicated by a greater time in target after midnight. The favourable effect on glucose control persisted during the morning even after closed-loop was discontinued and usual CSII was resumed at 08:00, with increased time in target and reduced time in hyperglycaemia.

### Closed-loop insulin delivery after evening meal and alcohol

Twelve further adults with type 1 diabetes were evaluated during overnight closed-loop insulin delivery following a larger evening meal and moderate amount of alcohol, associated with postprandial hyperglycaemia and delayed hypoglycaemia, re-

Figure 7.1: Summary of results of closed-loop studies




**Notes:** Data are displayed in box plots as median and interquartile range, for overall study periods. Target range for the 'Feasibility' study and the 'Alcohol & meal' study was 3.9 – 8.0 mmol/l. Target range for the 'Pregnancy' study was 3.5 – 7.8 mmol/l.[120]

spectively. Even after such challenges, closed-loop increased time in target glucose, reduced time spent hyperglycaemic and lowered glucose variability. There was a trend towards less time spent hypoglycaemic during closed-loop, and no episodes of hypoglycaemia after midnight.

### Daytime closed-loop insulin delivery during pregnancy

Closed-loop insulin delivery was evaluated in twelve pregnant women with type 1 diabetes during normal daily activities including moderate intensity exercise. Compared with conventional CSII, there was no difference in overall time spent in tar-

get range for pregnancy between 3.5 and 7.8 mmol/l, with even tighter control achieved overnight. The favourable glucose results achieved during CSII visits may be attributed to the well-controlled cohort of women studied (baseline HbA1c 6.4%). Closed-loop lowered the time spent below 2.5 mmol/l and the low blood glucose index. Hypoglycaemia occurred during both closed-loop and CSII visits, predominantly following moderate intensity exercise, although closed-loop prevented nocturnal episodes.

### Energy expenditure and glucose control in pregnancy

This evaluation provided the first objective evidence on activity patterns and energy expenditure in combination with sensor glucose in ten pregnant (mean gestation 19 weeks) women with type 1 diabetes during free-living. Glucose levels were above recommended targets for pregnancy with almost a third of the day spent hyperglycaemic. In comparison, during the 24 hour study in hospital, involving a controlled diet and structured low and moderate intensity exercise, glucose control was significantly improved. Moderate intensity exercise was achieved without any discomfort, but did result in hypoglycaemia despite efforts to reduce basal insulin infusion and consume additional carbohydrates.

### Sensor accuracy during exercise in pregnancy

The performance of a current generation CGM was objectively assessed, using plasma glucose as reference, in 12 pregnant women with type 1 diabetes during normal daily activities. Accuracy, measured by the median relative absolute difference between paired sensor and plasma glucose values, was lower during moderate intensity exercise (brisk treadmill walking) in the afternoon (20%) and morning (17%) compared with sedentary conditions (12%). Using Clarke error grid analysis, 14% of sensor glucose measurements during exercise were considered clinically unsafe, compared with 4% at rest. The reduced accuracy was only partly explained by the higher rate of change of glucose associated with physical activity.

## 7.2 Strengths

A major strength of my studies was the robust methodology. This included a crossover repeated measures design whereby each participant completed both a closed-loop

and a control visit under identical conditions, allowing for objective assessment of closed-loop without confounders such as inter-individual variability in insulin sensitivity. In addition, the randomised order of visits minimised any potential influence due to adjustment in insulin regimens between visits, as a result of information gained from the first study visit. There is only one other overnight closed-loop study published to date, carried out in 20 adults with type 1 diabetes using a model predictive control algorithm developed *in silico*.[105] This study was non-randomised as the open loop visit always took place first in order to provide the algorithm with meal information prior to closed-loop execution, hence there was a potential for human (subject and staff) learning.

Another strength is the direct applicability of the results to clinical practice, as the closed-loop was used under conditions as close to real life as possible. Commercially available glucose sensors and insulin pumps, delivering a routinely used rapid acting insulin analogue, were used for all studies. Subjects wore a single sensor during all study visits, which is likely to increase user acceptability and is more representative of real life. Previously reported closed-loop studies used at least two sensors, switching to a better performing sensor if accuracy became suboptimal.[83; 85; 101; 105; 111] Use of multiple sensors was evaluated by Castle et al, demonstrating reduction in very large sensor errors and improved accuracy (mean relative absolute difference 11.6% versus 14.8%) with using four sensors simultaneously compared with a single sensor.[280] Redundancy was not affected by sensor placement within 7mm of each other. However, these findings have limited applicability in the outpatient setting where patients are unlikely to be willing to wear more than one CGM device. In my studies, the sensor was calibrated using fingerprick capillary glucose as patients would normally do at home, rather than venous glucose as used in other closed-loop studies.[84; 112] Calibration was performed at times specified by the manufacturer with no additional calibrations if suboptimal accuracy was detected.

Importantly, the model predictive control algorithm used in my studies considered only real-time sensor glucose measurements to generate the advice on insulin infusion rates, rather than venous glucose as employed in previous closed-loop studies.[112] Although more accurate than interstitial glucose, venous glucose sampling is more invasive with a risk of infection and bleeding, and is not practical for outpatient use of closed-loop. Subcutaneous CGM is a more feasible method of measuring glucose as part of a closed-loop system in the home setting.

The advice of the model predictive control algorithm was always adhered to during studies, suggesting that the system may be reliably used in the home setting

without any need to override the algorithm. In a recent multicentre closed-loop study the algorithm advice was not followed on four occasions due to concern of near-hypoglycaemia.[105]

Initiation of the algorithm is straightforward for the user, requiring entry of three parameters: weight, total daily insulin dose, and basal infusion rates. A high degree of inter- and intra-individual variability in insulin requirements often limits the optimal tailoring of conventional insulin regimens in patients with diabetes. The adaptive nature of the model predictive control algorithm enabled the closed-loop system to cope with these variations effectively by initialising insulin sensitivity (based on total daily insulin dose and usual basal requirements) and adapting this estimate in real-time on the basis of sensor glucose measurements, resulting in safe and effective insulin dosing.

The effect of different start times of closed-loop insulin delivery on overnight glycaemic control was observed in the 'Feasibility' and 'Alcohol and meal' adult studies. Glucose levels from midnight appeared to be better controlled when closed-loop was commenced at 19:00 compared with a later start at 22:00. This was most likely associated with the increasing efficacy of closed-loop with longer duration of use. No difference in early (18:00) versus later (21:00) start of automated closed-loop was observed in a recent randomised study in eight young children.[106]

A major advantage of the model predictive control algorithm used is the reduction in hypoglycaemia, by suspending insulin delivery when sensor glucose is low or declining rapidly. The overall improvement in hypoglycaemia during closed-loop visits is significant as one of the greatest concerns for patients and their families is the fear of going low, especially overnight whilst asleep and in patients with reduced hypoglycaemia awareness or those living alone. This risk may be amplified further following situations such as drinking alcohol. In addition, treatment of hypoglycaemia may result in rebound hyperglycaemia, and repeated episodes may lead to avoidance behaviours such as under-insulinising or excessive snacking which could adversely affect glycaemic control.

The threshold chosen for treatment of hypoglycaemia was 3.0 mmol/l, which is lower than the glucose level normally used to define hypoglycaemia in clinical practice (4.0 mmol/l). This threshold was chosen to test the ability of closed-loop to prevent impending hypoglycaemia, in a controlled inpatient setting. The treatment was oral carbohydrate, consistent with management of hypoglycaemia in the outpatient setting. Intravenous dextrose was only indicated if subjects failed to recover from an episode after oral therapy, unlike in a previous closed-loop study where dextrose

was given if glucose was below 3.3 mmol/l.[83] In my studies, none of the episodes of hypoglycaemia required treatment with intravenous dextrose, in both adults and pregnant women.

Importantly, the improvements in glycaemic control during closed-loop were achieved with no difference in the average amount of insulin infused on closed-loop and CSII visits, further substantiated by similar measured plasma insulin concentrations. This is a clinically significant outcome as excess exogenous insulin therapy may be associated with weight gain, and further emphasises the benefit of glucose-responsive insulin delivery.

A single insulin pump was used for all study visits. Minor differences between commercially available pumps, including precision of basal infusion rates and frequency of bolus pulses which may affect insulin delivery, have been reported. Aspart insulin was used for all visits, to ensure comparability of results of plasma insulin concentration as the assay varies for different types of insulin. On arrival for each visit, the participant's usual pump was replaced with the study pump using the same infusion site. An established subcutaneous insulin infusion site was ideally used on all study visits, thus minimising the possibility of variable delivery of insulin associated with recent set change. Insertion of a catheter into subcutaneous tissue results in an inflammatory reaction affecting local blood flow, which in turn may affect absorption of insulin.

Another strong point of my studies was the standardisation of meals and snacks consumed. All meals were prepared on site in the hospital kitchen, and matched in carbohydrate and macronutrient content during closed-loop and CSII interventions. Subjects chose from a variety of meals, which were carefully selected to represent what might normally be consumed at home. Other closed-loop studies used liquid meal replacements such as Ensure Plus in place of normal meals.[105]

Plasma glucose was measured using the gold standard YSI 2300 STAT Plus analyser (YSI Ltd, Fleet, UK). Whole blood was centrifuged immediately after sampling. Plasma was separated from whole blood, and either frozen for retrospective analysis of glucose ('Feasibility' study) or measured in real-time ('Alcohol and meal' and pregnancy studies). A delay in separation of plasma from whole blood may result in deterioration of glucose concentrations.[281]

## 7.3 Limitations

One of the limitations of my studies was the lack of automation of the closed-loop system, which required entry of CGM readings into the computer and subsequent manual alteration of pump settings every 15 minutes by the research nurse or clinician. The possibility of operator error in carrying out this repetitive process cannot be excluded, as well as the likelihood of delays in manually changing the pump. This approach is not feasible in clinical practice, and requires development of an automated closed-loop system with wireless transmission of data. Such a system has been evaluated in eight children overnight in an inpatient setting, demonstrating safe and efficacious control of automated closed-loop insulin delivery.[106]

All of the studies had a 'control' visit where subjects remained on their usual CSII regimen. Although this visit replicated the home setting most closely, subjects anecdotally reported better/worse glycaemic control at home despite maintaining an identical CSII regimen. The reasons for this are likely to be multi-factorial including day to day variability in insulin sensitivity, differences in meals consumed which are less regulated at home, and variable activity levels. One of the main limitations of carrying out clinic-based studies is that subjects tend to be more sedentary, which is likely to have an influence on daytime glucose control, although in a similar manner on both closed-loop and CSII visits. This effect was observed in the 24-hour study in pregnant women with type 1 diabetes, where a greater time was spent sedentary compared with during free-living. Interestingly, in the feasibility study in adults, there were seven episodes of hypoglycaemia despite subjects being less active.

Another potential limitation of the closed-loop system employed in my studies is the requirement for manual calculation of prandial insulin boluses, which may be viewed as extra effort for some patients who envisage using a closed-loop system with minimal user inputs, and additionally depends on the accuracy of the method used (bolus wizard calculator or carbohydrate to insulin ratios). Although inaccurate estimation of mealtime insulin boluses may have affected postprandial glycaemic control, a similar method of calculation was used on both study visits, hence ensuring comparability between closed-loop and conventional CSII.

Because of the nature of the medical devices used, the interventions were known to both participants and investigators. Subjects were blinded to CGM and plasma glucose taken during the study. Investigators were blinded to plasma glucose values in the 'Feasibility' study, but not in the other two studies for safety reasons.

As the order of study visits was revealed to each subject on attending for their

first night, any self-adjustment of insulin regimens between visits may potentially have affected glycaemic control on the second night. However, this bias was largely overcome by randomly allocating participants to their order of completion of study visits. It is impossible to exclude an effect of intra-individual variability in insulin sensitivity associated with multiple factors such as physical activity, concurrent illness, and menstrual cycle in females between visits.

The subjects enrolled to the studies were all educated insulin pump users of white ethnicity, hence were not representative of all adults with type 1 diabetes. Additionally, more motivated patients tend to volunteer for research trials. Although only small numbers were studied, these trials were designed to evaluate the feasibility of closed-loop insulin delivery. This should be taken into account when considering the results of multiple secondary analyses performed. Additionally, the observations obtained may limit applicability to all patients with type 1 diabetes.

## 7.4 Future studies

The immediate benefits of short-term (up to 48 hours) application of closed-loop on glycaemic control have been demonstrated in several studies carried out in a controlled environment. Although the clinical research facility is the safest setting for evaluating feasibility and performance of closed-loop, limitations exist which may only be overcome by moving to outpatient testing over a longer period. This necessitates an automated closed-loop system with wireless data transmission.

A multicentre randomised controlled study evaluating overnight closed-loop insulin delivery in 24 adults with type 1 diabetes in the home setting is planned. Patients already established on CSII and willing to use CGM and closed-loop will complete four weeks of CGM alone whilst maintaining their usual CSII regimen and four weeks of closed-loop insulin delivery overnight with 'open-loop' CSII and CGM during the daytime, in random order. The acceptability of closed-loop will be assessed with interviews and validated questionnaires measuring satisfaction and user-friendliness of the devices. Subjects will also complete a survey evaluating fears related to hypoglycaemia. This qualitative information will be invaluable in understanding the psychosocial aspects of using closed-loop and hence assist in developing better device training and support systems, as well as providing criteria to facilitate selection of those patients that are most likely to benefit from using the system.

Following on from this study, a larger study over a longer period, enabling assess-

ment of a sustained benefit of closed-loop insulin delivery on glycaemic control as measured by HbA1c and reduction in diabetes-related complications, is warranted. This will also be important for women with type 1 diabetes during pregnancy, as maintenance of glucose control throughout gestation would be expected to be associated with improved pregnancy outcomes.

Extending outpatient evaluation of overnight closed-loop insulin delivery to the daytime is justified. The study in pregnancy demonstrated the challenges in managing glucose levels following meals and physical activity, in a controlled setting. Testing in the home setting, where routines are much less structured, will provide important information on feasibility of using closed-loop in clinical practice. Results gained from physiological studies in progress, using stable isotope tracers to evaluate glucose fluxes following meals of varying sizes or nutrient composition, will aid in refining closed-loop algorithms.[282] Further clinical and simulation studies evaluating different intensities of exercise are required, to assist in our understanding of the variable glycaemic responses seen.

All the studies evaluating closed-loop insulin delivery thus far have been carried out in people with type 1 diabetes. Closed-loop is likely to have a similar beneficial effect in patients with type 2 diabetes. One indication in this patient cohort may be insulin therapy in hospital, where closed-loop insulin delivery is likely to provide safer glycaemic control. Currently, variable insulin replacement schedules including use of sliding scales in addition to infrequent blood glucose monitoring often result in suboptimal diabetes management in hospital. This can result in worse metabolic control, associated with poorer health outcomes and longer hospital stay.[283] A pilot feasibility study of closed-loop insulin delivery in patients with type 2 diabetes is underway. Twelve subjects, treated by oral glucose-lowering medications alone, are being studied on two separate 24-hour visits on the clinical research facility, comparing closed-loop glucose control with usual diabetes therapy. Subjects remain sedentary and consume regular meals and snacks, thus mimicking an inpatient stay. Following on from this, a larger study is planned in hospitalised patients with type 2 diabetes.

Another area of research is evaluating which patients are most likely to benefit from closed-loop glycaemic control. For safety reasons, my studies excluded patients with hypoglycaemia unawareness or history of severe hypoglycaemia. Evaluation of this group is warranted as the effect of closed-loop in reducing hypoglycaemia, as demonstrated in my studies in adults, is likely to have a significant impact on quality of life. Although closed-loop insulin delivery only had a limited impact in the cohort of pregnant women studied, women with suboptimal glucose control during

pregnancy are likely to realise a benefit.

## 7.5 Closed-loop insulin delivery in clinical practice

### 7.5.1 Challenges to implementation

#### 7.5.1.1 Glucose sensors

The development of closed-loop systems has progressed rapidly over the last decade, but has faced several hurdles, the major one being development of more accurate and reliable glucose sensors. Most of the commercially-available CGM devices still require confirmatory capillary glucose measurement prior to any action taken based on sensor values. Both delays in glucose sensing between interstitial and plasma compartments and errors in calibration contribute to inaccurate sensor readings and associated false alarms. Factory-based calibrations of future generation devices may limit the risk of human or meter error. Setting realistic expectations of the limitations of CGM will be vital to increasing patient satisfaction and reducing the risk of premature discontinuation.

#### 7.5.1.2 Insulin delivery

The subcutaneous-subcutaneous route is minimally invasive and hence has the most potential for closed-loop application in the outpatient setting. It is the approach employed in the majority of closed-loop systems currently under development, however is also associated with delays related to both glucose sensing and insulin kinetics.[93] One of the major limitations of subcutaneous insulin delivery is the delay in time to peak blood glucose lowering effect which may be $90-120$ minutes with the currently available rapid acting insulin analogues. In addition, the high degree of inter- and intra-individual variability in insulin absorption must also be considered.[67] Optimising the timing and mode of bolus delivery, together with ongoing development of faster more stable insulins that mimic more closely the actions of endogenous insulin may help overcome some of these hurdles. Alternative routes of insulin delivery, such as the intraperitoneal and transdermal routes, may provide another solution.

#### 7.5.1.3 Control algorithm

Ongoing efforts are required in refining control algorithms to be able to integrate the delays associated with glucose sensing and insulin delivery, particularly in the postprandial period. In addition, both inter- and intra-subject variability in glucose responses to factors such as meals, illness, stress, travel and physical activity will need to be incorporated into metabolic models in order to accurately predict glucose excursions.

Use of closed-loop during the day will require the ability to cope with such challenges as activities of daily living, meals and exercise, which result in transient derangements in glucose-insulin metabolism. Hyperglycaemia following carbohydrate ingestion is a major challenge to closed-loop. Delays in glucose sensing and subcutaneous insulin delivery limit the ability of closed-loop to slow the rapid rise in glucose postprandially. Moreover, a delay in insulin action as glucose levels are declining may result in late hypoglycaemia.

Exercise has longer lasting and more dynamic effects on glucose-insulin dynamics. The magnitude of effect depends on several factors, including duration and intensity of activity. Even low intensity daily tasks such as housework and shopping may lower glucose levels. Adjustment in insulin delivery according to exercise of different intensities will be required. Replicating the physiological hyperinsulinaemia following intense exercise will be a challenge for closed-loop control due to the risk of iatrogenic hypoglycaemia. Announcement of exercise is likely to be an essential component to enable timely decrease in insulin delivery. Inclusion of glucagon in a closed-loop system may limit exercise-related hypoglycaemia.

#### 7.5.1.4 Device-patient interface

Currently, insulin delivery and continuous glucose sensing are contained in separate devices and require two separate insertions. Approaches to combine insulin delivery and continuous glucose sensing into a single device are being developed.[284] The feasibility of administering insulin and measuring glucose at the same adipose tissue site was evaluated in healthy subjects, demonstrating stability of glucose levels at the site of insulin administration.[285] Such 'single-port' systems will halve the number of skin perforations required as well as the number of devices that need to be carried, which is likely to increase device acceptability and hence compliance with wear.[42] This is significant as compliance is associated with greater efficacy of CGM. A recent meta-analysis demonstrated a 0.15% reduction in HbA1c for each extra day of sensor

wear.[286]

Development of an integrated user friendly system employing wireless data transmission will be important for outpatient use of closed-loop. Daytime application in particular will require the devices to be portable and discreet. Safety and efficacy of a prototype fully-automated closed-loop system using wireless transmission of data has been demonstrated overnight in eight young children in an inpatient setting.[106]

### 7.5.2 Patient selection

Appropriate patient selection for use of closed-loop will be essential. This may be guided by known predictors of success with currently used devices. Higher HbA1c, younger age and shorter diabetes duration were associated with greater benefit on CSII.[55] The UK National Institute for Health and Clinical Excellence judge CSII to be cost-effective in patients with persistently elevated HbA1c levels of 8.5% or higher. A meta-analysis of CGM showed the greatest benefit was seen in patients with higher HbA1c; 0.9% reduction when baseline HbA1c was 10%.[286] High frequency of SMBG testing and older age have also been linked with success on CGM.[25]

Closed-loop is likely to be most beneficial in patients who struggle to achieve glucose targets, and/or where further intensification of insulin regimens is limited by recurrent episodes of hypoglycaemia. Closed-loop may be a safer option for certain vulnerable patient groups including those with hypoglycaemia unawareness and those living alone. It is also likely to be indicated for patients who are less able to self-manage their diabetes, such as young children or those with learning disabilities, and where compliance is a barrier such as during adolescence.

Closed-loop may be indicated in women with type 1 diabetes during pregnancy where hypoglycaemia often limits safe achievement of tight glycaemic control. Selection of women most likely to benefit could be based on presence of known risk factors, including history of severe hypoglycaemia, hypoglycaemia unawareness, longer diabetes duration and lower HbA1c in early pregnancy.[176]

Future use of a closed-loop system will depend on patients' willingness to learn and their ability to use the technology. Patient acceptance is likely to be high, based on qualitative assessments carried out in adult patients [287] and caregivers of children with type 1 diabetes.[288] However, for some patients the benefits will be outweighed by the burdens and complexities of learning to use a new technology. Similar to the concerns expressed by patients on CGM, these may include dealing with alarms, body image issues related to permanently wearing a device, and pain with

insertion, which may limit acceptability of using closed-loop.[42]

### 7.5.3 Stepwise introduction

The future deployment of closed loop systems is likely to be a staged process, with the aims of improving glycaemic control and reducing hypoglycaemia whilst ensuring preservation of safety at each stage. This is most likely to commence with a closed-loop system that shuts off at low glucose levels. This feature is already available in the Paradigm Veo (Medtronic, Northridge, CA, USA), approved for commercial use in Europe since 2009 but awaiting authorisation in the USA. The pump can be linked with a glucose sensor, suspending insulin delivery for up to two hours during hypoglycaemia, but still demands manual calculation and entry of basal rates and boluses. In 2010, JDRF announced a partnership with Animas Corporation to develop a partially automated 'hypoglycaemia-hyperglycaemia minimiser' closed-loop system within the next four years, which will slow or stop insulin delivery when sensor glucose levels are declining and similarly increase insulin when rising until glucose returns to acceptable range.

The next feasible step may be using the closed-loop system overnight when meals and exercise do not confound glycaemic control, with the added significant benefit of preventing nocturnal hypoglycaemia. Daytime closed-loop glucose control will be more challenging. A hybrid or semi-closed loop system with meal announcement may be the most feasible approach, until delays in glucose sensing and subcutaneous insulin delivery can be overcome.

Closed-loop insulin delivery during exercise is potentially a safer and more flexible treatment option enabling patients to exercise with more confidence, however refinements and further testing, including simulation studies, will be required prior to safe application. Incorporation of motion sensors and heart rate monitoring into closed-loop systems is being considered.[236] The latter will require differentiation between transient (e.g. stress-induced), and substantial increases in heart rate. The Cellnovo (London, UK) insulin patch pump, due to be launched in Europe in late 2012, has an in-built accelerometer. Future systems may incorporate glucagon and/or other hormones.

The ultimate goal is an integrated system facilitating fully automated closed-loop control over 24 hours. These technological advances are important but should not delay gradual introduction of closed-loop into clinical practice.

### 7.5.4 Practical issues

Prior to employment of closed-loop systems in clinical practice, strict safety checks by regulatory bodies are essential, as technical faults or failure can lead to serious complications including severe hypoglycaemia due to excess insulin. Ongoing safety monitoring to manage technical issues will be necessary. Ensuring security and integrity of such technology-dependent systems will also be critical to guaranteeing safe use of closed-loop.

Telemedicine will increasingly play an integral role in closed-loop systems, allowing logging of data and enabling retrospective analysis and fine tuning of the system.[289] Distant monitoring of blood glucose will provide an added safety layer, above that embedded into the control algorithm. Global positioning system technology may be incorporated in a portable closed-loop system, enabling monitoring from any location. Such an application, termed E911, has been proposed as a tool for tracking and alerting medical personnel to impending hypoglycaemic events in patients at higher risk such as those with hypoglycaemia unawareness.[290]

In order to ensure the availability of closed-loop in clinical practice, both the initial expenses and the cost of ongoing consumables and maintenance must be taken into consideration. Closed-loop should ideally be available to all eligible patients regardless of economic circumstances and geographic location. More realistically, in many countries it is likely that product use will ultimately rely upon national health care policies based on cost-benefit analyses, and reimbursement schemes by health insurance companies.

Success of the artificial pancreas will also depend on the establishment of appropriate infrastructures that will sustain the ongoing deployment of the system. These include training courses for healthcare professionals and patients, a support network to manage the technological aspects, and collaboration with the industries producing the device and regulatory authorities to ensure availability and affordability.

## 7.6 Contribution to knowledge and concluding remarks

Diabetes is a condition where the body's innate ability to regulate blood glucose fails, instead relying on the individual's conscious efforts to maintain glycaemic control. Day-to-day variability in insulin requirements, which may be influenced by multiple factors, make such 'open-loop' control challenging. Even with the sophisticated insulin pumps and continuous glucose monitoring devices available currently, the ma-

jority of patients struggle to achieve optimal glycaemic control. Extensive efforts by clinicians and patients are still required. The 'closed-loop' or artificial pancreas system offers a more convenient and effective mode of insulin delivery, thus minimising the need for constant monitoring and adjustment. This may have a significant impact on patients' perceptions of their diabetes, including a reduced burden of self-care and increased self-confidence in achieving glucose targets without fear of hypoglycaemia.

These are the first randomised controlled studies evaluating closed-loop insulin delivery in adults and pregnant women with type 1 diabetes, using commercially available devices and a model predictive control algorithm. The results are summarised in Figure 7.1. In adults, overnight closed-loop resulted in safe and effective glycaemic control. These results were sustained even with evening consumption of a large meal and alcohol. In a cohort of well-controlled women during pregnancy, closed-loop insulin delivery during normal daily activities was as effective as conventional pump therapy. Safety of glucose control during closed-loop was maintained even after exercise of moderate intensity, with fewer episodes of hypoglycaemia overall and prevention of nocturnal episodes. The analysis of activity patterns and glycaemic control during free-living contributes to the understanding of the relationship between diet, exercise and glucose levels, which may be useful in future closed-loop systems incorporating accelerometry. This information may also be helpful to clinicians in optimising conventional treatment regimens, including formulation of exercise guidelines. The observations of lower accuracy of CGM during exercise will be important for patients to consider when exercising, and additionally in the development of closed-loop systems for daytime use.

In conclusion, my studies provide evidence of the safety and efficacy of closed-loop insulin delivery in adults with type 1 diabetes, including women during pregnancy, in a controlled setting. These results facilitate the transition to outpatient studies to assess performance over consecutive nights under real life conditions. Further system refinements will be necessary prior to optimal daytime application of closed-loop. As the hurdles and practicalities are gradually overcome, the ultimate goal of introduction of closed-loop in clinical practice will be realised.

# Appendix A

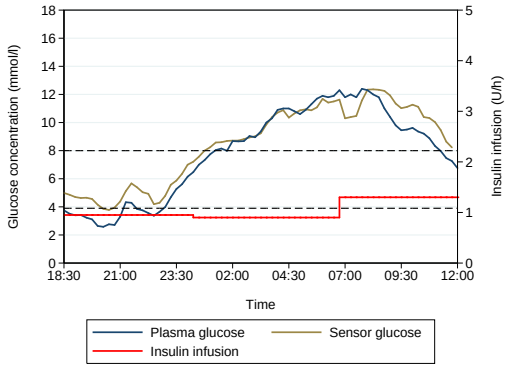
# Individual glucose & insulin profiles

This Appendix presents sensor glucose, plasma glucose and basal insulin profiles for all subjects on both their closed-loop and CSII study visits. Profiles for the 'Feasibility' study presented in Chapter 2 are shown in A.1. In relation to that study, subject 9 withdrew participation after their first visit and was replaced by subject 13. Profiles for the 'Alcohol and meal' study presented in Chapter 3 are shown in A.2, and for the 'Pregnancy' study presented in Chapter 4 in A.3. Each figure displays the CSII visit (left panel) and the closed-loop visit (right panel) for each subject. Meals and snacks consumed during the study with concurrent prandial insulin boluses administered are detailed in the table below each figure.

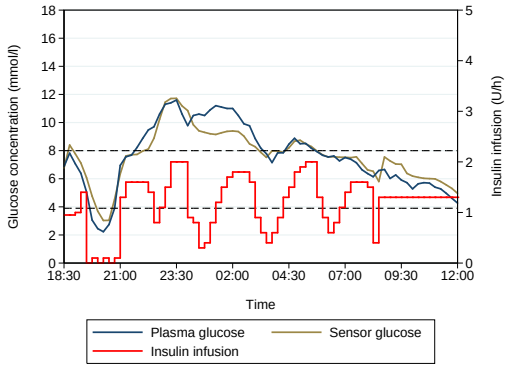
# A.1 Feasibility study

Subject 1

(a) CSII visit




(b) Closed-loop visit

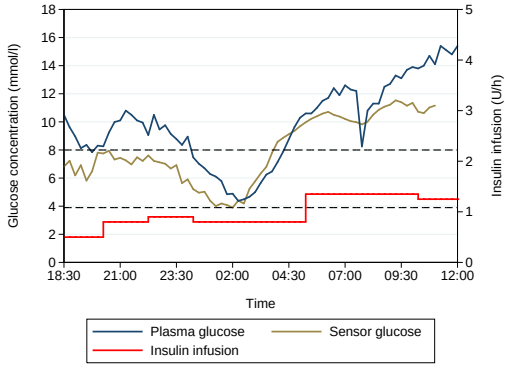



| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 19:00 | 80 | 19:00 | 6.6 |
| | 08:00 | 30 | 08:00 | 4.4 |
| Closed-loop | 19:00 | 80 | 19:00 | 6.6 |
| | 08:00 | 30 | 08:00 | 2.7 |

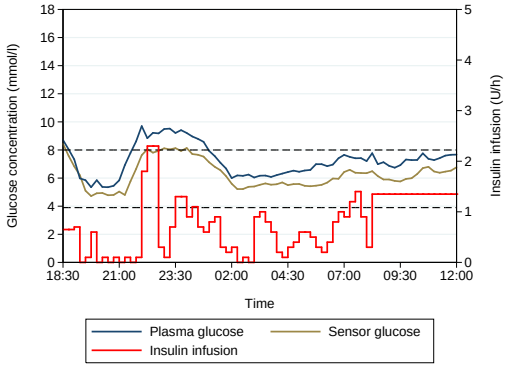
## A.1. FEASIBILITY STUDY

### Subject 2

(a) CSII visit



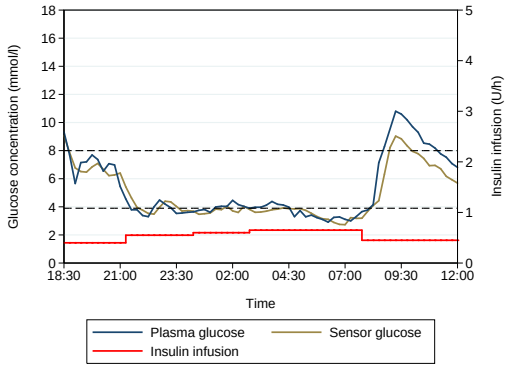

(b) Closed-loop visit



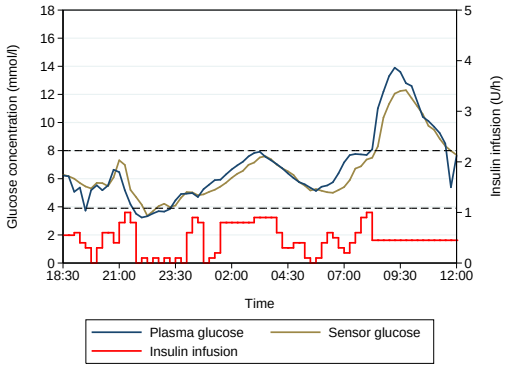

| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 19:00 | 60 | 19:00 | 6.0 |
| | 08:00 | 38 | 08:00 | 2.5 |
| Closed-loop | 19:00 | 60 | 19:00 | 6.0 |
| | 08:00 | 38 | 08:00 | 2.5 |

### Subject 3

(a) CSII visit




(b) Closed-loop visit

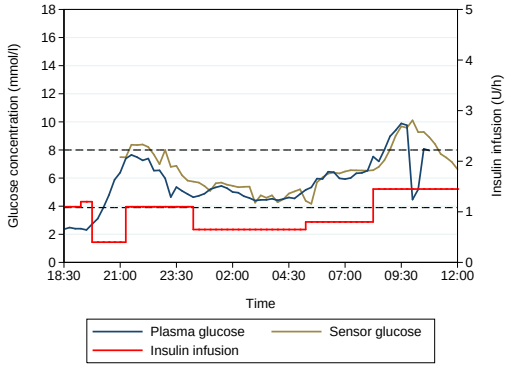



| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 19:00 | 60 | 19:00 | 4.6 |
| | 08:00 | 27 | 08:00 | 1.5 |
| Closed-loop | 19:00 | 60 | 19:00 | 4.6 |
| | 08:00 | 27 | 08:00 | 2.5 |

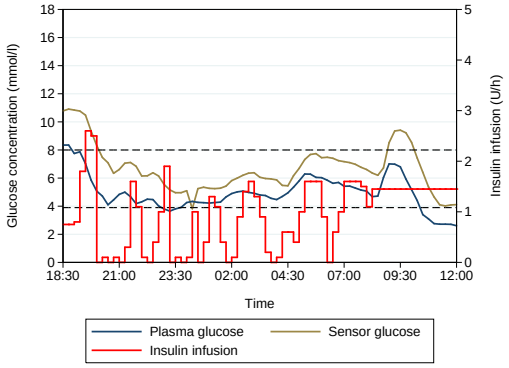
## A.1. FEASIBILITY STUDY

### Subject 4

(a) CSII visit



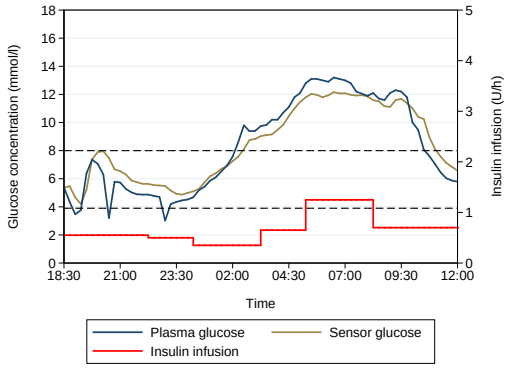

(b) Closed-loop visit



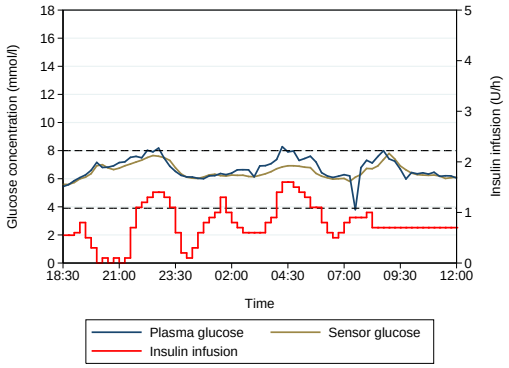

| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 19:00 | 60 | 19:00 | 5.0 |
| | 08:00 | 44 | 08:00 | 3.7 |
| Closed-loop | 19:00 | 60 | 19:00 | 7.5 |
| | 08:00 | 44 | 08:00 | 3.7 |

### Subject 5

(a) CSII visit




(b) Closed-loop visit

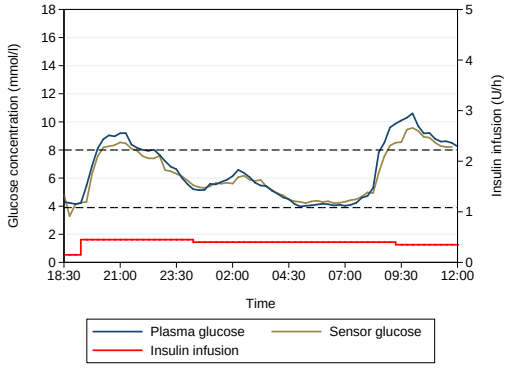



| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 19:00 | 60 | 19:30 | 7.5 |
| | 08:00 | 38 | 08:00 | 9.0 |
| Closed-loop | 19:00 | 60 | 19:00 | 7.5 |
| | 08:00 | 38 | 08:00 | 6.5 |

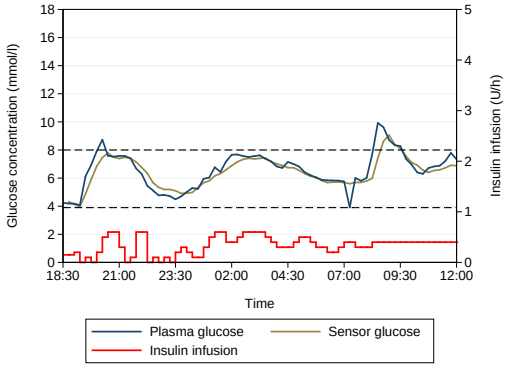
## A.1. FEASIBILITY STUDY

### Subject 6

(a) CSII visit



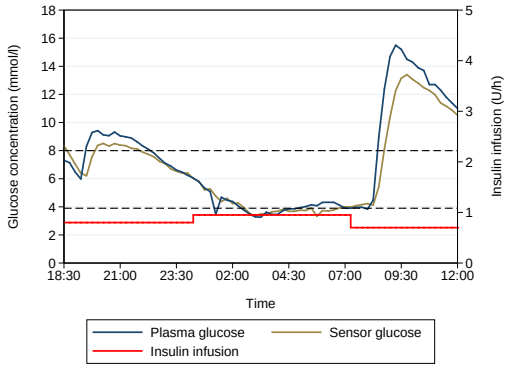

(b) Closed-loop visit



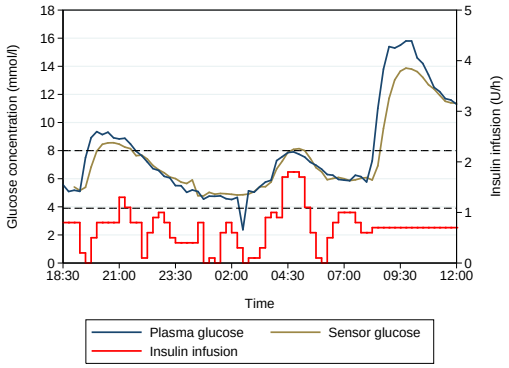

| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 19:00 | 60 | 19:00 | 4.8 |
| | 08:00 | 40 | 08:00 | 3.5 |
| Closed-loop | 19:00 | 60 | 19:00 | 4.8 |
| | 08:00 | 40 | 08:00 | 3.5 |

### Subject 7

(a) CSII visit




(b) Closed-loop visit

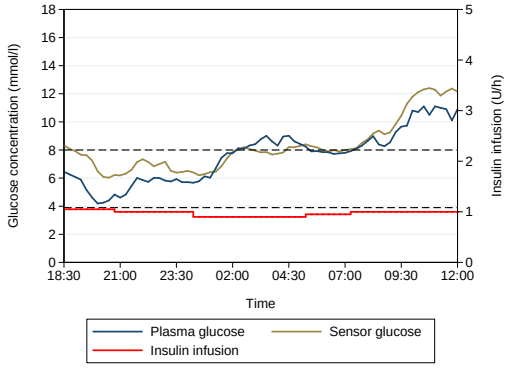



| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 19:00 | 60 | 19:00 | 4.0 |
| | 08:00 | 74 | 08:00 | 6.0 |
| Closed-loop | 19:00 | 60 | 19:00 | 5.0 |
| | 08:00 | 74 | 08:00 | 6.0 |

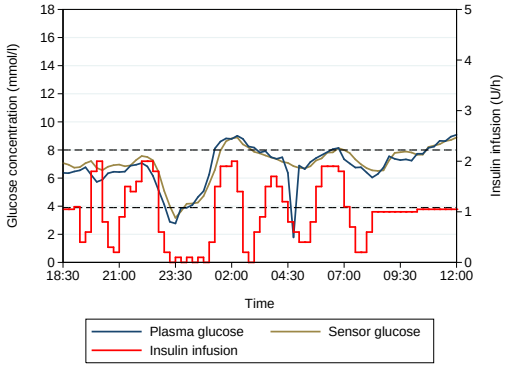
## A.1. FEASIBILITY STUDY

### Subject 8

(a) CSII visit



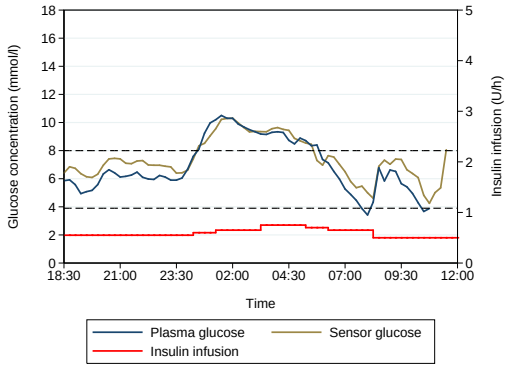

(b) Closed-loop visit



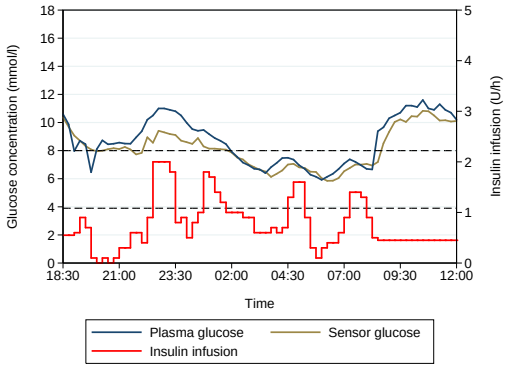

| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 19:00 | 60 | 19:00 | 6.0 |
| | 08:00 | 34 | 08:00 | 4.5 |
| Closed-loop | 19:00 | 60 | 19:00 | 6.0 |
| | 08:00 | 34 | 08:00 | 3.3 |

### Subject 10

(a) CSII visit




(b) Closed-loop visit

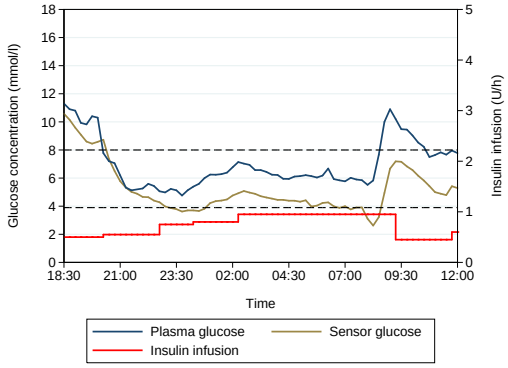



| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 19:00 | 60 | 19:00 | 5.0 |
| | 08:00 | 50 | 08:00 | 3.5 |
| Closed-loop | 19:00 | 45 | 19:00 | 6.0 |
| | 08:00 | 50 | 08:00 | 6.0 |

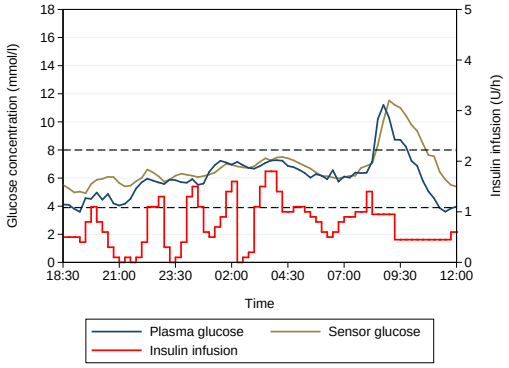
## A.1. FEASIBILITY STUDY

### Subject 11

(a) CSII visit



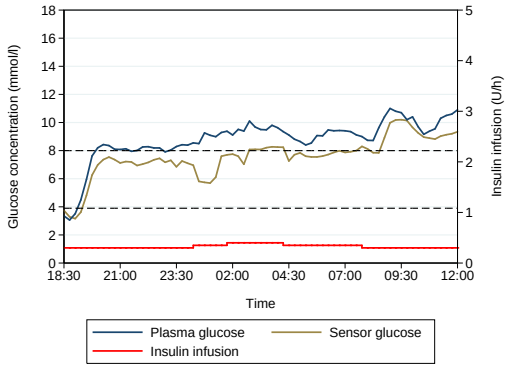

(b) Closed-loop visit



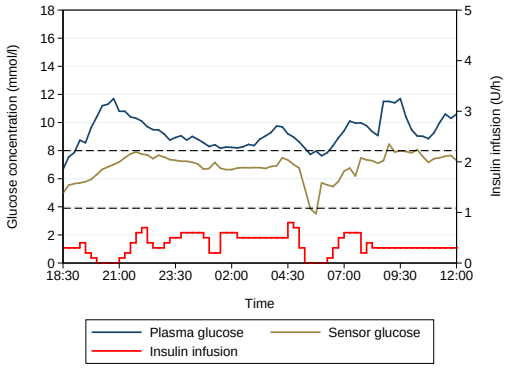

| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 19:00 | 60 | 19:00 | 3.1 |
| | 08:00 | 67 | 08:00 | 5.0 |
| Closed-loop | 19:00 | 60 | 19:00 | 4.5 |
| | 08:00 | 67 | 08:00 | 5.8 |

### Subject 12

(a) CSII visit




(b) Closed-loop visit

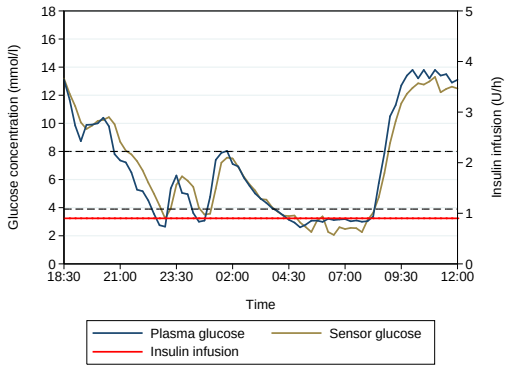



| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 19:00 | 60 | 19:20 | 3.5 |
| | 08:00 | 64 | 08:00 | 2.3 |
| Closed-loop | 19:00 | 60 | 19:00 | 4.0 |
| | 08:00 | 64 | 08:00 | 2.4 |

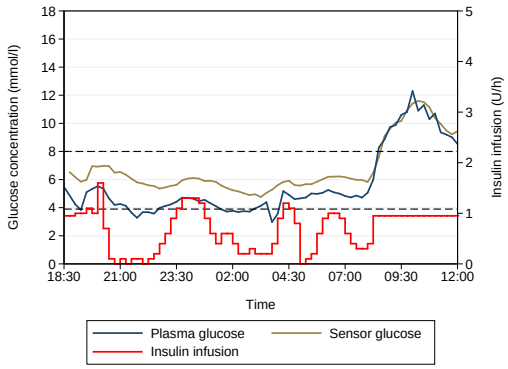
## A.1. FEASIBILITY STUDY

Subject 13

(a) CSII visit




(b) Closed-loop visit

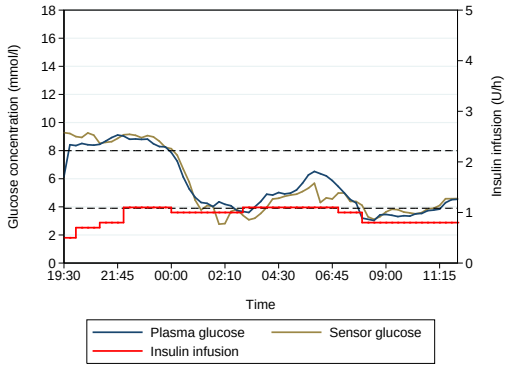



| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 19:00 | 60 | 19:00 | 6.0 |
| | 08:00 | 64 | 08:00 | 4.5 |
| Closed-loop | 19:00 | 60 | 19:00 | 4.5 |
| | 08:00 | 64 | 08:00 | 6.5 |

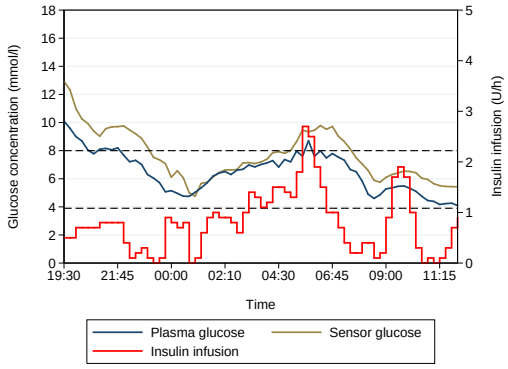
## A.2 Meal and alcohol study

Subject 1

(a) CSII visit



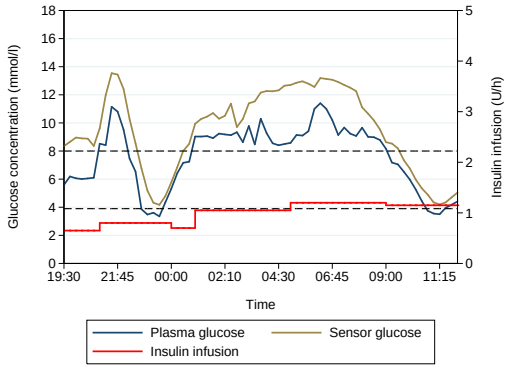

(b) Closed-loop visit



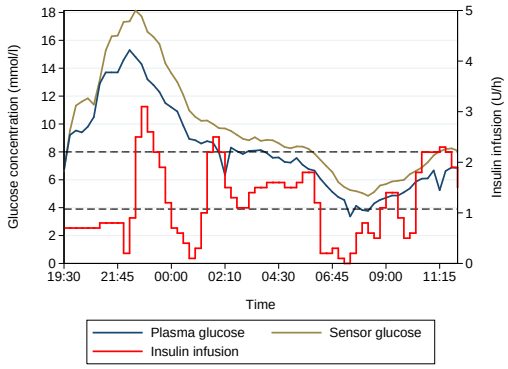

| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 20:30 | 118 | 20:30 | 12.5 |
| Closed-loop | 20:30 | 118 | 20:30 | 12.5 |

Subject 2

(a) CSII visit




(b) Closed-loop visit

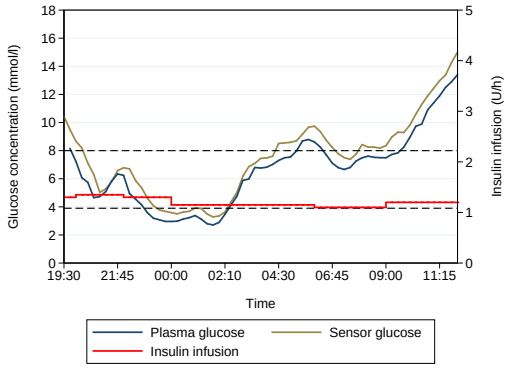



| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 20:30 | 107 | 20:30 | 14.2 |
| Closed-loop | 20:30 | 107 | 20:30 | 14.0 |

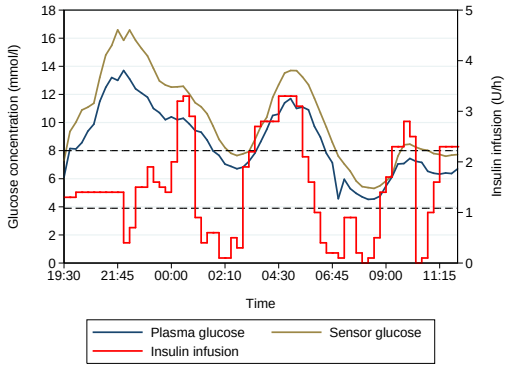
## A.2. MEAL AND ALCOHOL STUDY

### Subject 3

(a) CSII visit



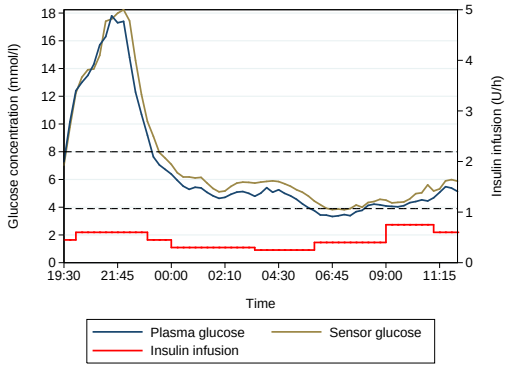

(b) Closed-loop visit



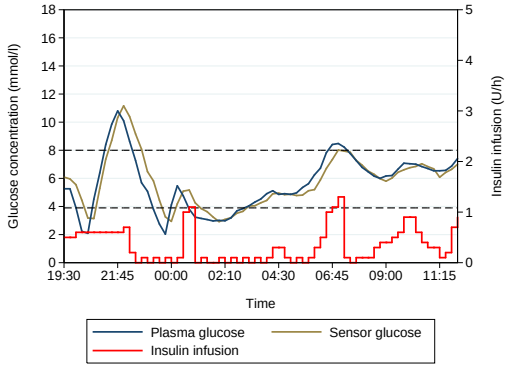

| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 20:30 | 118 | 20:30 | 11.5 |
| Closed-loop | 20:30 | 118 | 20:50 | 12.2 |

### Subject 4

(a) CSII visit




(b) Closed-loop visit

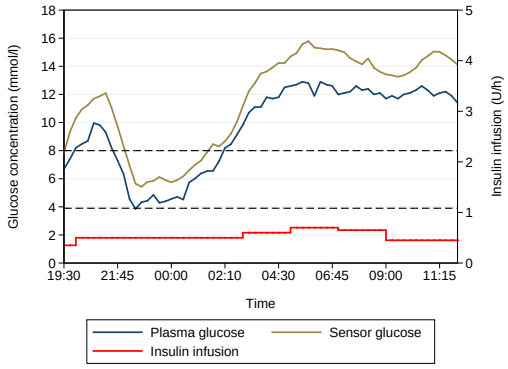



| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 20:30 | 116 | 20:45 | 10.0 |
| Closed-loop | 20:30 | 116 | 21:00 | 7.5 |

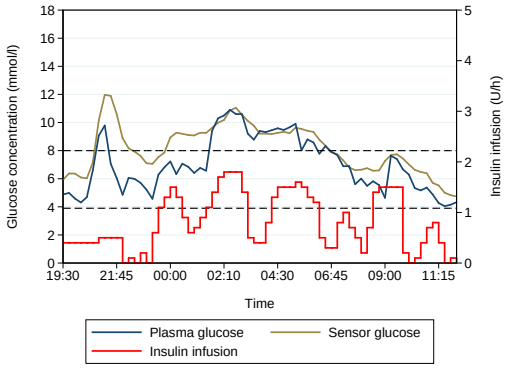
## A.2. MEAL AND ALCOHOL STUDY

### Subject 5

(a) CSII visit



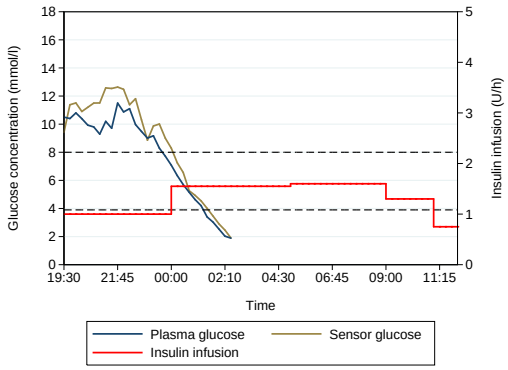

(b) Closed-loop visit



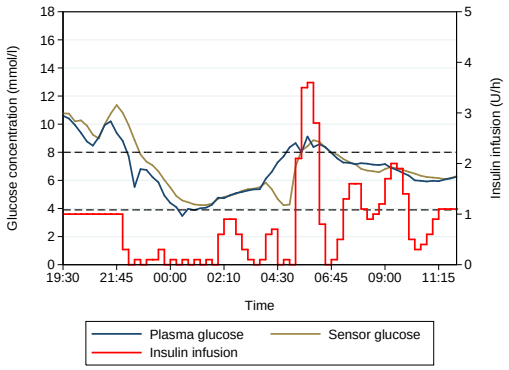

| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 20:30 | 100 | 20:30 | 8.5 |
| Closed-loop | 20:30 | 100 | 20:45 | 7.5 |

### Subject 6

(a) CSII visit




(b) Closed-loop visit

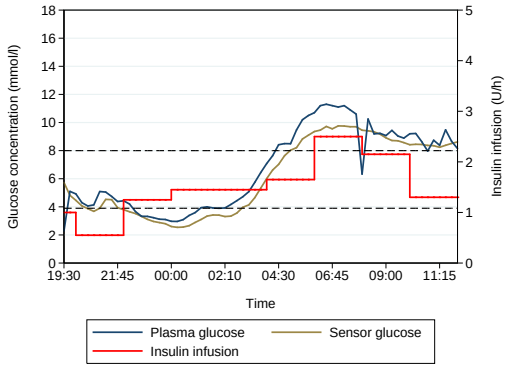



| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 20:30 | 100 | 20:30 | 24.0 |
| Closed-loop | 20:30 | 100 | 20:45 | 24.0 |

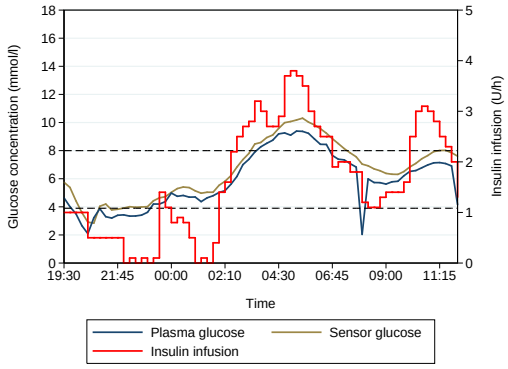
## A.2. MEAL AND ALCOHOL STUDY

### Subject 7

(a) CSII visit



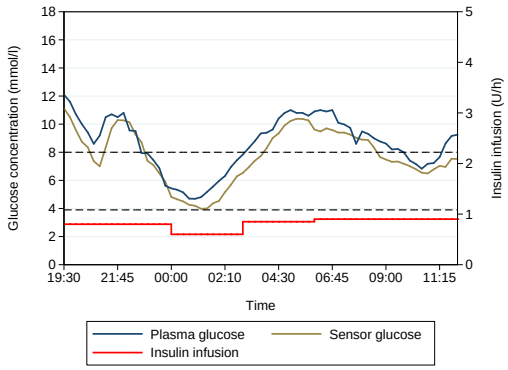

(b) Closed-loop visit



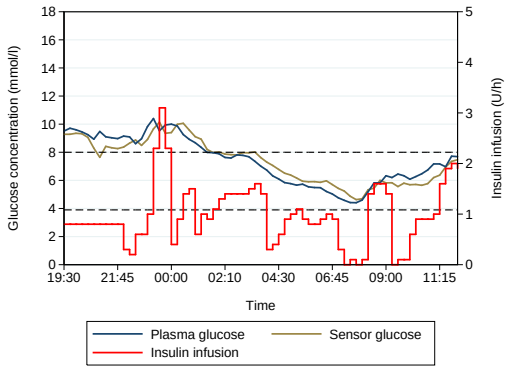

| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 20:30 | 100 | 21:15 | 10.0 |
| Closed-loop | 20:30 | 100 | 21:00 | 7.0 |

### Subject 8

(a) CSII visit




(b) Closed-loop visit

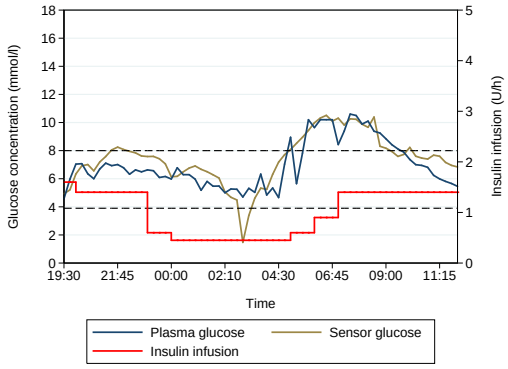



| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 20:30 | 100 | 20:30 | 10.0 |
| Closed-loop | 20:30 | 100 | 20:30 | 9.0 |

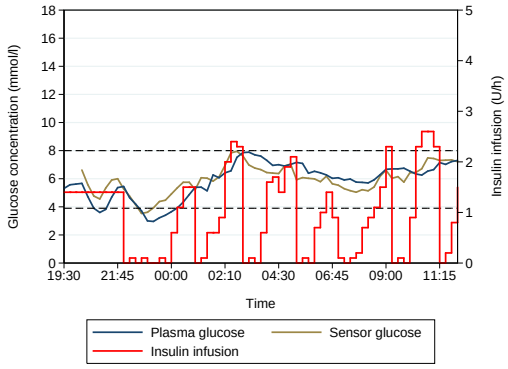
## A.2. MEAL AND ALCOHOL STUDY

### Subject 9

(a) CSII visit



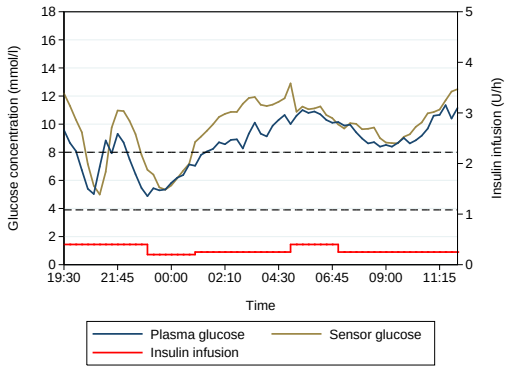

(b) Closed-loop visit



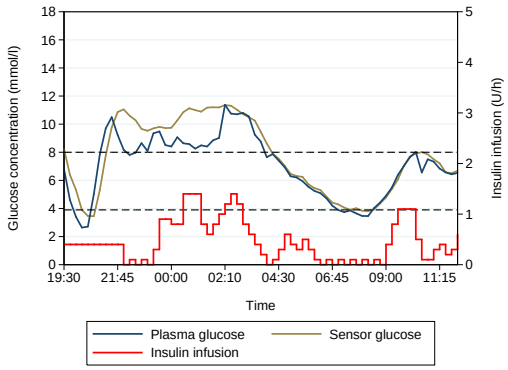

| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 20:30 | 100 | 20:30 | 8.3 |
| Closed-loop | 20:30 | 100 | 21:00 | 8.3 |

### Subject 10

(a) CSII visit




(b) Closed-loop visit

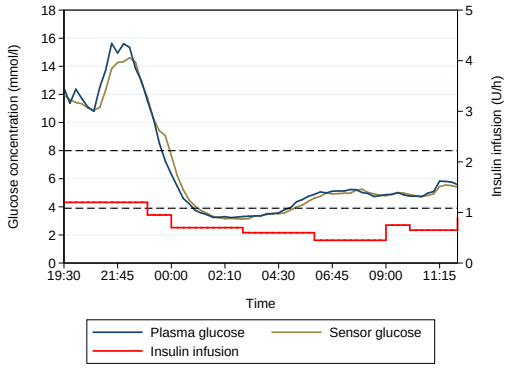



| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 20:30 | 100 | 20:30 | 8.0 |
| Closed-loop | 20:30 | 100 | 21:00 | 6.0 |

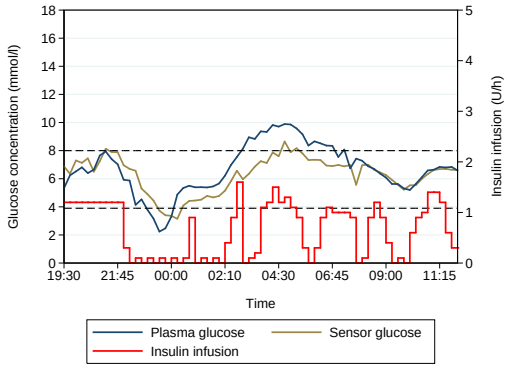
## A.2. MEAL AND ALCOHOL STUDY

### Subject 11

(a) CSII visit



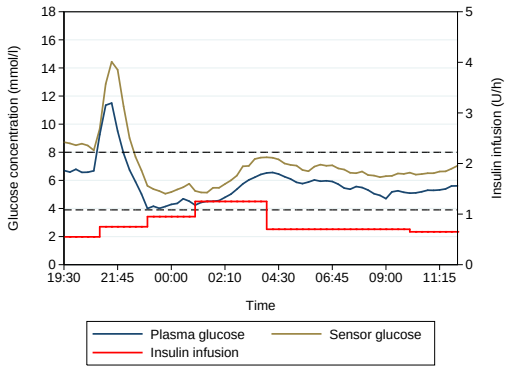

(b) Closed-loop visit



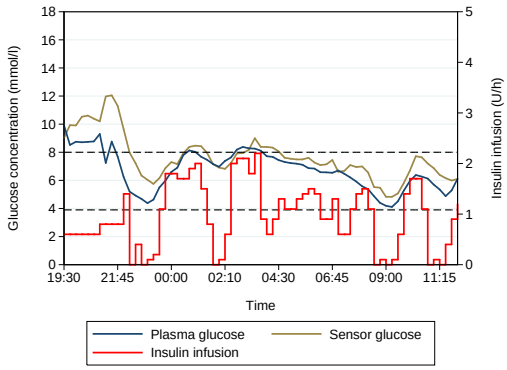

| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 20:30 | 100 | 20:30 | 8.5 |
| Closed-loop | 20:30 | 100 | 20:30 | 9.0 |

### Subject 12

(a) CSII visit




(b) Closed-loop visit

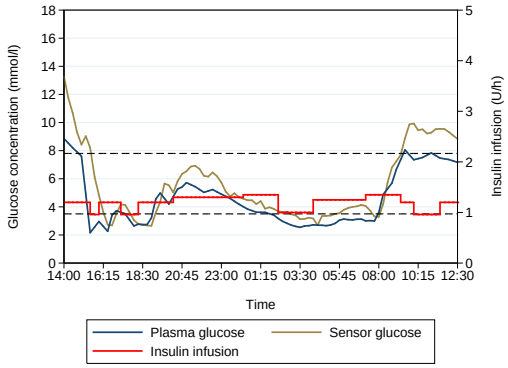



| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 20:30 | 100 | 21:00 | 14.4 |
| Closed-loop | 20:30 | 100 | 20:30 | 14.9 |

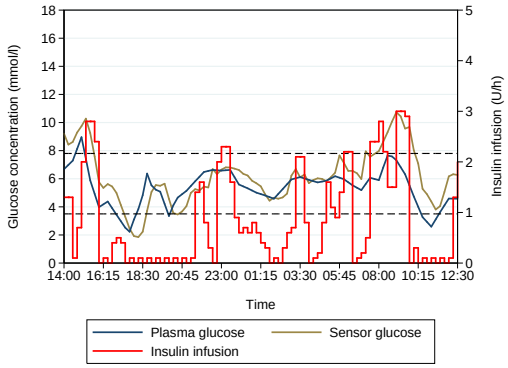
# A.3 Pregnancy study

Subject 1

(a) CSII visit




(b) Closed-loop visit

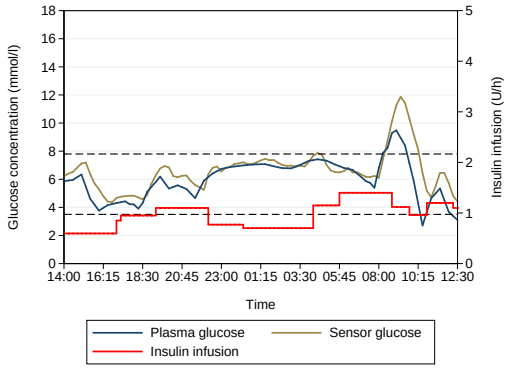



| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 14:30 | 15 | 14:30 | 0.5 |
| | 18:00 | 60 | 17:50 | 4.8 |
| | 21:00 | 15 | 21:00 | 1.5 |
| | 07:30 | 50 | 07:50 | 3.7 |
| Closed-loop | 14:30 | 15 | 14:30 | 1.5 |
| | 18:00 | 60 | 18:10 | 4.6 |
| | 07:30 | 50 | 07:30 | 5.6 |

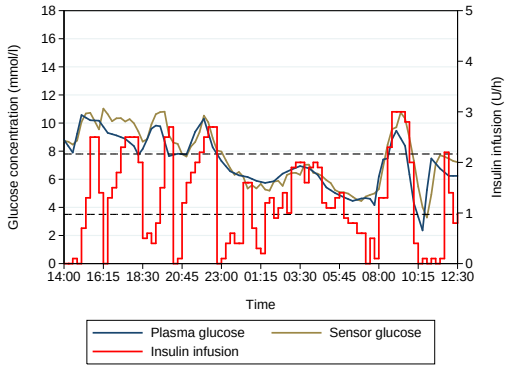
## A.3. PREGNANCY STUDY

Subject 2

(a) CSII visit




(b) Closed-loop visit

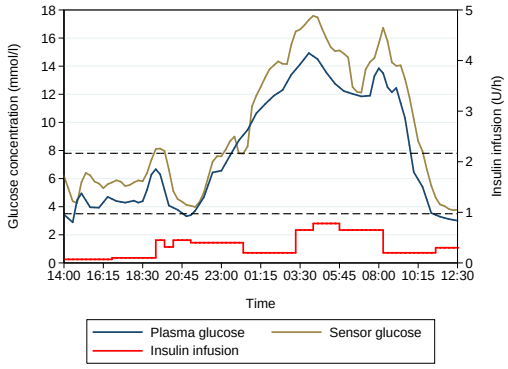



| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 18:00 | 60 | 18:10 | 4.6 |
| | 07:30 | 50 | 07:30 | 5.6 |
| Closed-loop | 18:00 | 60 | 17:50 | 9.5 |
| | 21:00 | 15 | 21:00 | 1.5 |
| | 07:30 | 50 | 07:50 | 3.7 |
| | 09:00 | 15 | 09:00 | 2.3 |

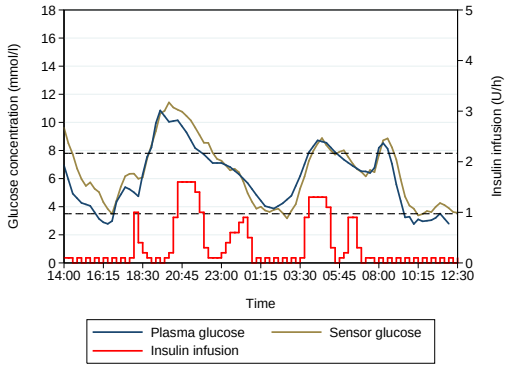
## A.3. PREGNANCY STUDY

### Subject 3

(a) CSII visit



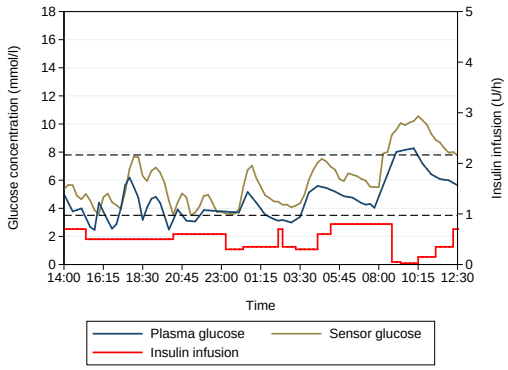

(b) Closed-loop visit



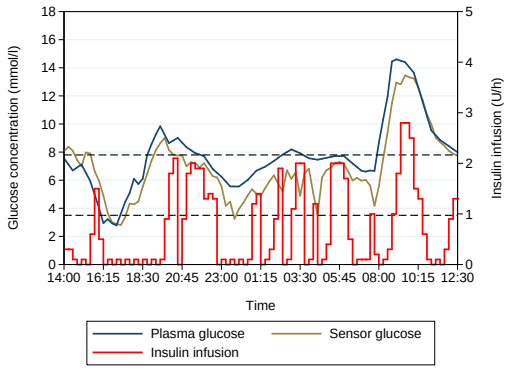

| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 18:00 | 60 | 17:50 | 6.9 |
| | 07:30 | 50 | 07:20 | 8.6 |
| | 09:00 | 15 | 09:00 | 2.3 |
| Closed-loop | 18:00 | 60 | 17:50 | 7.0 |
| | 21:00 | 15 | 21:00 | 1.5 |
| | 07:30 | 50 | 07:25 | 7.7 |

### Subject 4

(a) CSII visit




(b) Closed-loop visit

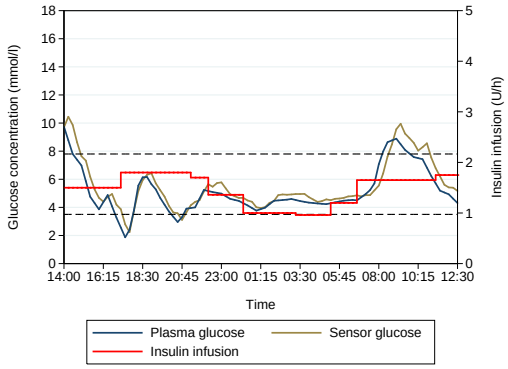



| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 18:00 | 60 | 17:55 | 12.0 |
| | 07:30 | 50 | 07:30 | 5.0 |
| Closed-loop | 18:00 | 60 | 17:50 | 12.0 |
| | 07:30 | 50 | 07:20 | 8.0 |

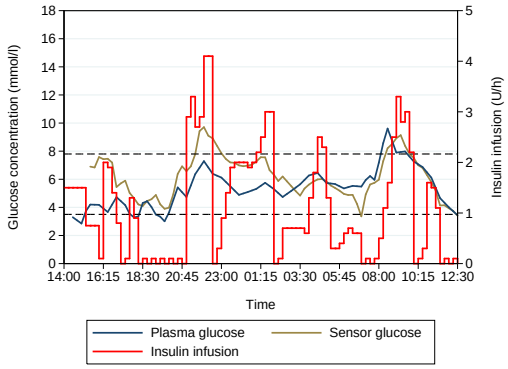
## A.3. PREGNANCY STUDY

Subject 5

(a) CSII visit




(b) Closed-loop visit

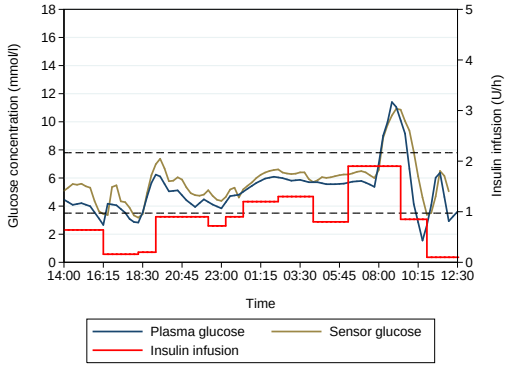



| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 18:00 | 60 | 18:15 | 4.0 |
| | 07:30 | 50 | 07:35 | 6.1 |
| | 09:00 | 15 | 09:00 | 1.0 |
| Closed-loop | 18:00 | 60 | 17:55 | 10.0 |
| | 07:30 | 50 | 07:25 | 11.0 |
| | 09:00 | 15 | 09:00 | 2.0 |

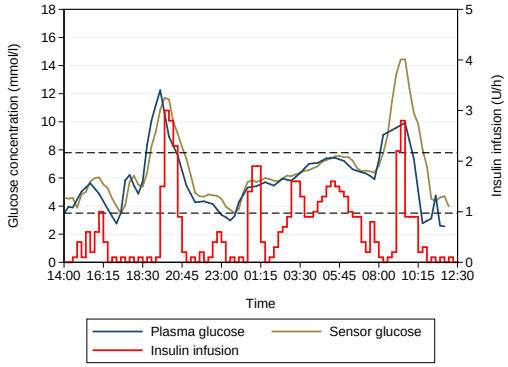
## A.3. PREGNANCY STUDY

### Subject 6

(a) CSII visit



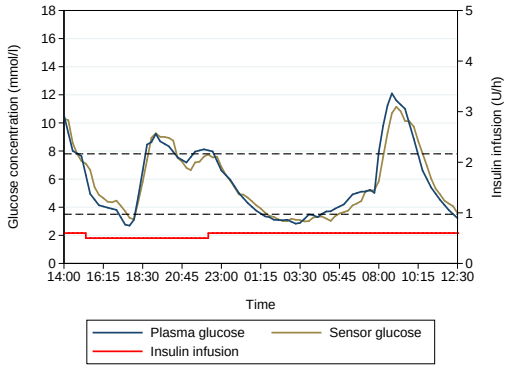

(b) Closed-loop visit



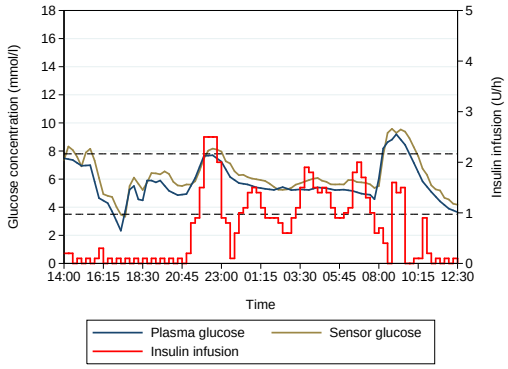

| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 18:00 | 60 | 18:05 | 8.2 |
| | 07:30 | 50 | 07:20 | 16.6 |
| Closed-loop | 18:00 | 60 | 17:50 | 7.6 |
| | 21:00 | 15 | 21:00 | 0.5 |
| | 07:30 | 50 | 07:25 | 9.2 |

### Subject 7

(a) CSII visit




(b) Closed-loop visit

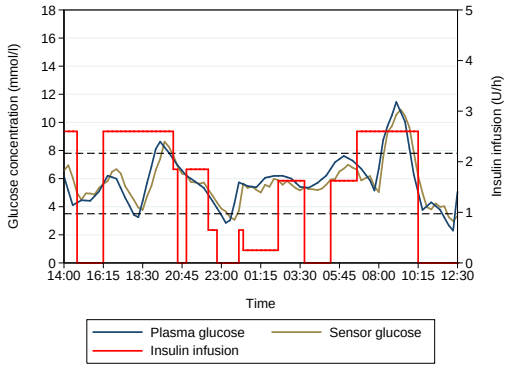



| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 18:00 | 60 | 18:00 | 4.5 |
| | 07:30 | 50 | 07:20 | 4.0 |
| Closed-loop | 18:00 | 60 | 17:50 | 9.5 |
| | 07:30 | 50 | 07:20 | 8.0 |

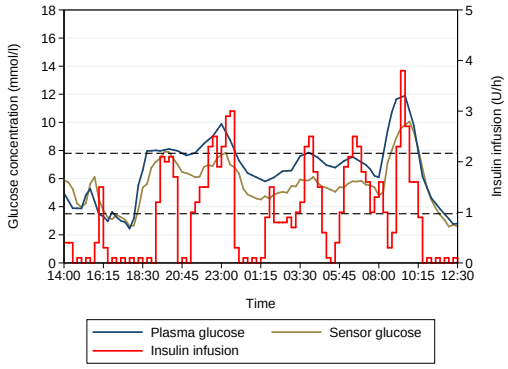
## A.3. PREGNANCY STUDY

### Subject 8

(a) CSII visit



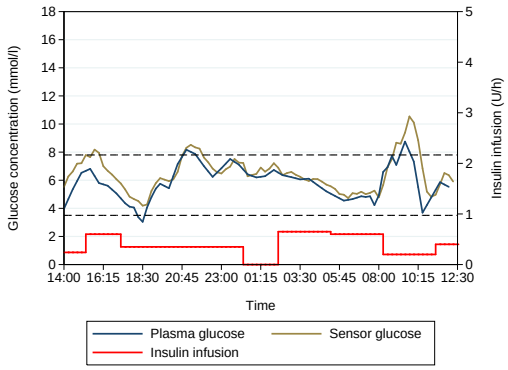

(b) Closed-loop visit



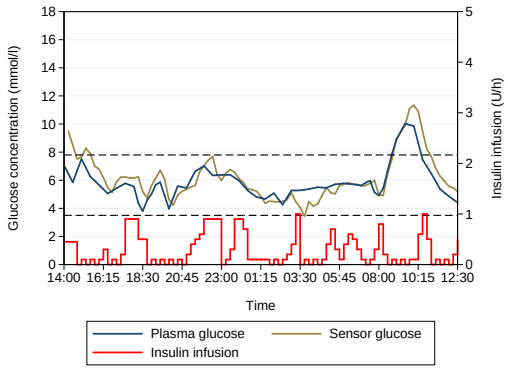

| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 18:00 | 60 | 17:50 | 6.0 |
| | 07:30 | 50 | 07:20 | 9.0 |
| | 09:00 | 30 | 09:00 | 3.0 |
| Closed-loop | 18:00 | 60 | 18:00 | 6.0 |
| | 07:30 | 50 | 07:25 | 9.0 |

### Subject 9

(a) CSII visit




(b) Closed-loop visit

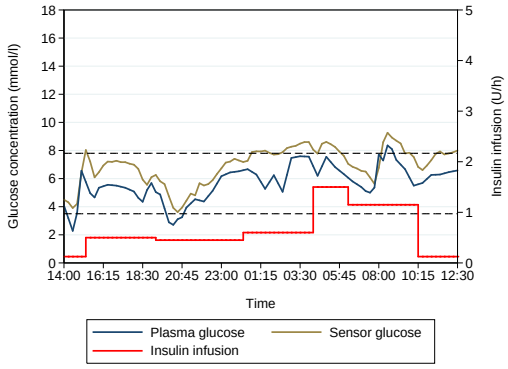



| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 18:00 | 60 | 17:55 | 4.6 |
| | 07:30 | 50 | 07:20 | 3.6 |
| | 09:00 | 30 | 09:00 | 1.3 |
| Closed-loop | 18:00 | 60 | 17:50 | 5.3 |
| | 07:30 | 50 | 07:20 | 4.7 |

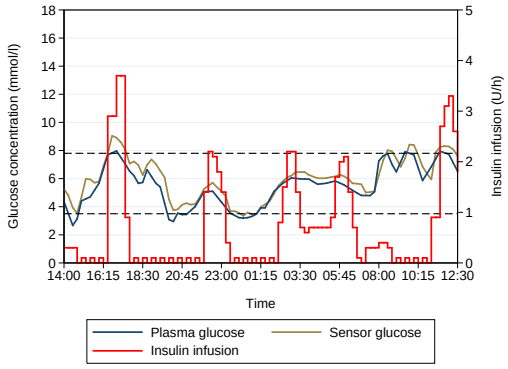
## A.3. PREGNANCY STUDY

### Subject 10

(a) CSII visit



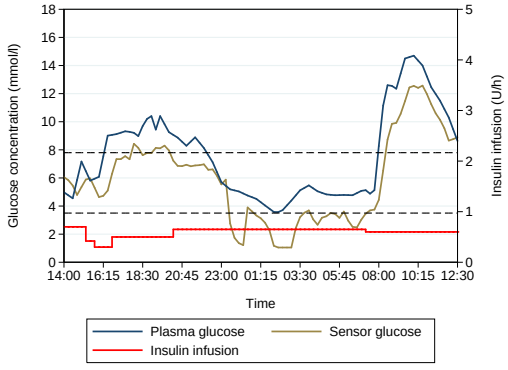

(b) Closed-loop visit



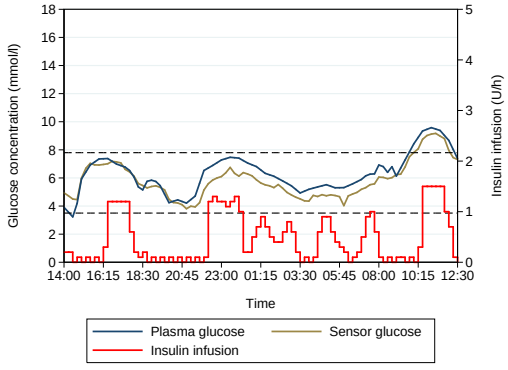

| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 18:00 | 60 | 17:50 | 12.0 |
| | 07:30 | 50 | 07:20 | 7.9 |
| Closed-loop | 18:00 | 60 | 17:50 | 18.0 |
| | 07:30 | 50 | 07:25 | 11.0 |

### Subject 11

(a) CSII visit




(b) Closed-loop visit

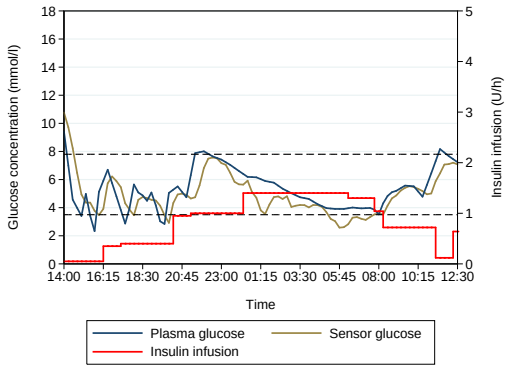



| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 18:00 | 60 | 17:50 | 7.2 |
| | 21:00 | 15 | 21:00 | 1.8 |
| | 07:30 | 50 | 07:30 | 2.4 |
| | 09:00 | 15 | 09:00 | 1.5 |
| Closed-loop | 18:00 | 60 | 17:50 | 5.5 |
| | 07:30 | 50 | 07:20 | 5.9 |

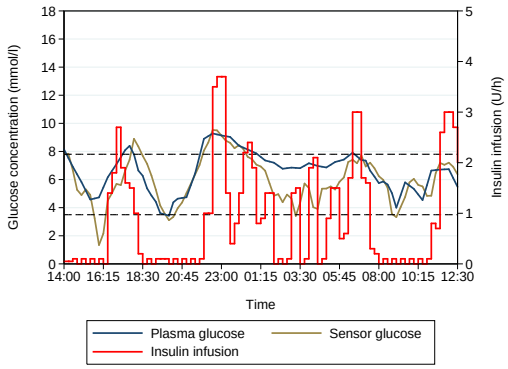
## A.3. PREGNANCY STUDY

Subject 12

(a) CSII visit




(b) Closed-loop visit




| Visit | Time | Carbohydrates (g) | Time | Insulin bolus (U) |
|---|---|---|---|---|
| CSII | 18:00 | 60 | 18:00 | 14.9 |
| | 07:30 | 50 | 07:30 | 12.0 |
| Closed-loop | 18:00 | 60 | 17:50 | 16.0 |
| | 07:30 | 50 | 07:20 | 14.0 |

# Appendix B

# Achievements

## Publications

- Haidar A, Elleri D, Allen J, Harris J, Kumareswaran K, Nodale M, Acerini C, Wilinska M, Jackson N, Umpleby M, Evans M, Dunger D, Hovorka R. "Validity of Triple and Dual-Tracer Techniques to Estimate Glucose Appearance" *American Journal of Physiology Endocrinology & Metabolism* 2012 Mar 27

- Kumareswaran K, Evans M, Hovorka R. "Closed-loop insulin delivery: towards improved diabetes care" *Discovery Medicine* 2012 Feb, 13(69):159-70

- Kumareswaran K, Elleri D, Allen J, Harris J, Xing D, Kollman C, Nodale M, Murphy H, Amiel S, Heller S, Wilinska M, Acerini C, Evans M, Dunger D, Hovorka R. "Meta-analysis of overnight closed-loop randomised studies in children and adults with type 1 diabetes: the Cambridge cohort" *Journal of Diabetes Science and Technology* 2011 Nov, 5(6):1352-62

- Murphy H, Kumareswaran K, Elleri D, Allen J, Caldwell K, Biagioni M, Simmons D, Dunger D, Nodale M, Wilinska M, Amiel S, Hovorka R. "Safety and efficacy of 24-hour closed-loop insulin delivery in well controlled pregnant women with type 1 diabetes: a randomised crossover case series" *Diabetes Care* 2011 Dec, 34(12):2527-9

- Hovorka R, Kumareswaran K, Harris J, Allen J, Elleri D, Xing D, Kollman C, Nodale M, Murphy H, Dunger D, Amiel A, Heller S, Wilinska M, Evans M.

"Overnight closed-loop insulin delivery (artificial pancreas) in adults with type 1 diabetes: crossover randomised controlled studies" *British Medical Journal* 2011 Apr, 342:d1855

- Kumareswaran K, Evans M, Hovorka R. "Artificial Pancreas: an emerging approach to treat type 1 diabetes" *Expert Review of Medical Devices* 2009 July, 6(4):401-410

## Awards & prizes

- John Stowers Research Award (best conference poster), EASD Diabetic Pregnancy Study Group meeting 2011
- MRL Student Symposium poster prize, University of Cambridge Metabolic Research Laboratories 2011
- Class of 2011 Endocrine Trainee Travel Award, ENDO Boston 2011
- Juvenile Diabetes Research Foundation Student Research Gold Award (best conference poster), Diabetes Technology Meeting 2010
- Travel Award, European Association for the Study of Diabetes meeting 2010
- Eli Lilly Award (best clinical science poster), Diabetes UK Annual Professional Conference 2010
- Travel Award, Diabetes UK Annual Professional Conference 2010

## Formal presentations

- "Physical activity energy expenditure and glucose levels in pregnant women with type 1 diabetes during free-living and controlled conditions" (poster) American Diabetes Association, Philadelphia USA, 2012
- "Continuous glucose monitoring performance during exercise in pregnant women with type 1 diabetes" (poster) American Diabetes Association, Philadelphia USA, 2012

- “Closed-loop insulin delivery during normal daily activities in pregnant women with type 1 diabetes" (oral) Advanced Technologies and Treatments for Diabetes, Barcelona Spain, 2012
- “Closed-loop insulin delivery during normal daily activities in pregnant women with type 1 diabetes" (poster) Medical Research Society Clinician Scientists in Training Meeting, London UK, 2012
- “Closed-loop insulin delivery protects against nocturnal hypoglycaemia after moderate physical activity in pregnant women with type 1 diabetes" (poster) EASD Diabetic Pregnancy Study Group meeting, Cambridge UK, 2011
- “The diverse spectrum of non-islet cell tumour-induced hypoglycaemia – 3 case reports” (poster) ENDO Annual Meeting, Boston USA, 2011
- “Overnight closed-loop insulin delivery in adults with type 1 diabetes” (poster) Parliamentary and Scientific Committee SET for BRITAIN Competition, House of Commons London UK, 2011
- “Closing the loop overnight in adults with type 1 diabetes following standard meal and large meal with alcohol” (oral) Advanced Technologies and Treatments for Diabetes, London UK, 2011
- “Overnight closed-loop insulin delivery in adults with type 1 diabetes” (poster) Medical Research Society Clinician Scientists in Training Meeting, London UK, 2011
- “A rare cause of hypoglycaemia” (oral) Addenbrooke’s Hospital Grand Round, Cambridge UK, 2010
- “Overnight closed-loop insulin delivery in adults with type 1 diabetes” (poster) Diabetes Technology Meeting, Bethesda USA, 2010
- “Overnight closed-loop glucose control following consumption of alcohol in adults with type 1 diabetes” (oral) European Association for the Study of Diabetes, Stockholm Sweden, 2010
- “Non-islet cell tumour-induced hypoglycaemia – what is the optimal treatment? 2 case reports” (poster) UK Ireland Neuroendocrine Tumour Society Meeting, Belfast Ireland, 2010

- "Overnight closed loop glucose control following consumption of alcohol in adults with type 1 diabetes" (oral) American Diabetes Association, Orlando USA, 2010
- "Closing the loop in adults with type 1 diabetes" (oral) Diabetes UK Annual Professional Conference, Liverpool UK, 2010
- "Closing the loop in adults with type 1 diabetes" (oral) Anglo Danish Dutch Diabetes Group Meeting, Avegoor Netherlands, 2009

# References


[1] A Guyton and J Hall. *Textbook of Medical Physiology*. Elsevier Saunders, Philadelphia, 11 edition, 2006. 1

[2] World Health Organization: Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: Report of a WHO/IDF consultation. Technical report, World Health Org, Geneva, 2006. 2, 88

[3] J. A. Todd. Etiology of type 1 diabetes. *Immunity*, 32(4):457–67, 2010. 2

[4] J. E. Shaw, R. A. Sicree, and P. Z. Zimmet. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Research and Clinical Practice*, 87(1):4–14, 2010. 2

[5] The NHS Information Centre. National diabetes audit executive summary 2009-2010. Key findings about the quality of care for people with diabetes in England and Wales. Technical report, 2011. 2, 12

[6] P. Zhang, X. Z. Zhang, J. Brown, D. Vistisen, R. Sicree, J. Shaw, and G. Nichols. Global healthcare expenditure on diabetes for 2010 and 2030. *Diabetes Research and Clinical Practice*, 87(3):293–301, 2010. 2

[7] American Diabetes Association. Executive summary: standards of medical care in diabetes – 2012. *Diabetes Care*, 35 Suppl 1:S4–10, 2012. 3, 12

[8] G. Freckmann, A. Baumstark, N. Jendrike, E. Zschornack, S. Kocher, J. Tshiananga, F. Heister, and C. Haug. System accuracy evaluation of 27 blood glucose monitoring systems according to DIN EN ISO 15197. *Diabetes Technol Ther*, 12(3):221–31, 2010. 3, 147

[9] D. C. Klonoff. Continuous glucose monitoring: roadmap for 21st century diabetes therapy. *Diabetes Care*, 28(5):1231–9, 2005. 3, 132

[10] W. L. Clarke, D. Cox, L. A. Gonderfrederick, W. Carter, and S. L. Pohl. Evaluating clinical accuracy of systems for self-monitoring of blood-glucose. *Diabetes Care*, 10(5):622–8, 1987. 3, 4, 37, 138

[11] ISO 15197:2003. In vitro diagnostic test systems: requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus. Technical report, 2003. 4, 137, 144

[12] K. Rebrin, G. M. Steil, W. P. Van Antwerp, and J. J. Mastrototaro. Subcutaneous glucose predicts plasma glucose independent of insulin: implications for continuous monitoring. *Am J Physiol Endocrinol Metab*, 277:E561–E571, 1999. 5

[13] N. Sachedina and J. C. Pickup. Performance assessment of the Medtronic-MiniMed Continuous Glucose Monitoring System and its use for measurement of glycaemic control in type 1 diabetic subjects. *Diabet Med*, 20(12):1012–5, 2003. 5

[14] M. Schoemaker, E. Andreis, J. Roper, R. Kotulla, V. Lodwig, K. Obermaier, P. Stephan, W. Reuschling, M. Rutschmann, R. Schwaninger, U. Wittmann, H. Rinne, H. Kontschieder, and W. Strohmeier. The SCGM1 System: subcutaneous continuous glucose monitoring based on microdialysis technique. *Diabetes Technol Ther*, 5(4):599–608, 2003. 5

[15] F. Valgimigli, F. Lucarelli, C. Scuffi, S. Morandi, and I. Sposato. Evaluating the clinical accuracy of GlucoMen(R)Day: a novel microdialysis-based continuous glucose monitor. *J Diabetes Sci Technol*, 4(5):1182–92, 2010. 5, 6, 11, 148

[16] B. Kovatchev, S. Anderson, L. Heinemann, and W. Clarke. Comparison of the numerical and clinical accuracy of four continuous glucose monitors. *Diabetes Care*, 31(6):1160–1164, 2008. 6, 7, 50, 53

[17] S. K. Garg, J. Smith, C. Beatson, B. Lopez-Baca, M. Voelmle, and P. A. Gottlieb. Comparison of accuracy and safety of the SEVEN and the Navigator continuous glucose monitoring systems. *Diabetes Technol Ther*, 11(2):65–72, 2009. 6, 133, 144

[18] D. B. Keenan, J. J. Mastrototaro, H. Zisser, K. A. Cooper, G. Raghavendhar, S. W. Lee, J. Yusi, T. Bailey, R. L. Brazg, and R. V. Shah. Accuracy of the Enlite 6-day glucose sensor with Guardian and Veo calibration algorithms. *Diabetes Technol Ther*, 14(3):225–31, Mar 2011. 6, 7, 10, 134

[19] R. O. Potts, J. A. Tamada, and M. J. Tierney. Glucose monitoring by reverse iontophoresis. *Diabetes Metab Res Rev*, 18 Suppl 1:S49–53, 2002. 5

[20] S. P. Newman, D. Cooke, A. Casbard, S. Walker, S. Meredith, A. Nunn, L. Steed, A. Manca, M. Sculpher, M. Barnard, D. Kerr, J. Weaver, J. Ahlquist, and S. J. Hurel. A randomised controlled trial to compare minimally invasive glucose monitoring devices with conventional monitoring in the management of insulin-treated diabetes mellitus (MITRE). *Health Technol Assess*, 13(28):1–194, 2009. 5

[21] A. Kamath, A. Mahalingam, and J. Brauker. Analysis of time lags and other sources of error of the DexCom SEVEN continuous glucose monitor. *Diabetes Technol Ther*, 11(11):689–95, 2009. 7, 10, 133, 134, 144, 148

[22] S. Vaddiraju, D. J. Burgess, I. Tomazos, F. C. Jain, and F. Papadimitrakopoulos. Technologies for continuous glucose monitoring: current problems and future promises. *J Diabetes Sci Technol*, 4(6):1540–62, 2010. 7, 148

[23] D. Deis, J. Bolinder, J. P. Riveline, T. Battelino, E. Bosi, N. Tubiana-Rufi, D. Kerr, and M. Phillip. Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. *Diabetes Care*, 29(12):2730–2, 2006. 7

[24] W. V. Tamborlane, R. W. Beck, B. W. Bode, B. Buckingham, H. P. Chase, R. Clemons, R. Fiallo-Scharer, L. A. Fox, L. K. Gilliam, I. B. Hirsch, E. S. Huang, C. Kollman, A. J. Kowalski, L. Laffel, J. M. Lawrence, J. Lee, N. Mauras, M. O'Grady, K. J. Ruedy, M. Tansey, E. Tsalikian, S. Weinzimer, D. M. Wilson, H. Wolpert, T. Wysocki, D. Y. Xing, and Continuous Juvenile Diabet Res Fdn. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *New Engl J Med*, 359(14):1464–U65, 2008. 7

[25] R. W. Beck, B. Buckingham, K. Miller, H. Wolpert, D. Xing, J. M. Block, H. P. Chase, I. Hirsch, C. Kollman, L. Laffel, J. M. Lawrence, K. Milaszewski, K. J. Ruedy, and W. V. Tamborlane. Factors predictive of use and of benefit from continuous glucose monitoring in type 1 diabetes. *Diabetes Care*, 32(11):1947–53, 2009. 7, 161

[26] G. Y. Gandhi, M. Kovalaske, Y. Kudva, K. Walsh, M. B. Elamin, M. Beers, C. Coyle, M. Goalen, M. S. Murad, P. J. Erwin, J. Corpus, V. M. Montori, and

M. H. Murad. Efficacy of continuous glucose monitoring in improving glycemic control and reducing hypoglycemia: a systematic review and meta-analysis of randomized trials. *J Diabetes Sci Technol*, 5(4):952–65, 2011. 7

[27] B. Bode, R. W. Beck, D. Xing, L. Gilliam, I. Hirsch, C. Kollman, L. Laffel, K. J. Ruedy, W. V. Tamborlane, S. Weinzimer, and H. Wolpert. Sustained benefit of continuous glucose monitoring on A1c, glucose profiles, and hypoglycemia in adults with type 1 diabetes. *Diabetes Care*, 32(11):2047–9, 2009. 8

[28] T. Battelino, M. Phillip, N. Bratina, R. Nimri, P. Oskarsson, and J. Bolinder. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. *Diabetes Care*, 34(4):795–800, 2011. 8

[29] E. A. Ryan and J. Germsheid. Use of continuous glucose monitoring system in the management of severe hypoglycemia. *Diabetes Technol Ther*, 11(10):635–9, 2009. 8

[30] T. T. Ly, J. Hewitt, R. J. Davey, E. M. Lim, E. A. Davis, and T. W. Jones. Improving epinephrine responses in hypoglycemia unawareness with real-time continuous glucose monitoring in adolescents with type 1 diabetes. *Diabetes Care*, 34(1):50–2, 2011. 8

[31] M. W. Langendam, Y. M. Luijf, L. Hooft, J. H. Devries, A. H. Mudde, and R. J. Scholten. Continuous glucose monitoring systems for type 1 diabetes mellitus. *Cochrane Database Syst Rev*, 1:CD008101, 2012. 8

[32] I. B. Hirsch, J. Abelseth, B. W. Bode, J. S. Fischer, F. R. Kaufman, J. Mastrototaro, C. G. Parkin, H. A. Wolpert, and B. A. Buckingham. Sensor-augmented insulin pump therapy: Results of the first randomized treat-to-target study. *Diabetes Technol Ther*, 10(5):377–83, 2008. 8

[33] R. M. Bergenstal, W. V. Tamborlane, A. Ahmann, J. B. Buse, G. Dailey, S. N. Davis, C. Joyce, T. Peoples, B. A. Perkins, J. B. Welsh, S. M. Willi, M. A. Wood, and STAR Study Grp. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. *New Engl J Med*, 363(4):311–320, 2010. 8, 30

[34] J. B. Buse, G. Dailey, A. A. Ahmann, R. M. Bergenstal, J. B. Green, T. Peoples, R. J. Tanenberg, and Q. Yang. Baseline predictors of A1c reduction in adults using sensor-augmented pump therapy or multiple daily injection therapy: The STAR 3 experience. *Diabetes Technol Ther*, 13(6):601–6, 2011. 8

[35] I. Conget, T. Battelino, M. Gimenez, H. Gough, J. Castaneda, and J. Bolinder. The SWITCH study (sensing with insulin pump therapy to control HbA1c): design and methods of a randomized controlled crossover trial on sensor-augmented insulin pump efficacy in type 1 diabetes suboptimally controlled with pump therapy. *Diabetes Technol Ther*, 13(1):49–54, 2011. 8

[36] I Conget, T Battelino, B Olsen, I Schütz-Fuhrmann, E Hommel, R Hoogma, U Schierloh, N Sulli, and J Bolinder. Efficacy of continuous glucose monitoring in type 1 diabetes sub-optimally controlled with insulin pump therapy. the SWITCH study. In *Advanced Technologies & Treatments for Diabetes, Barcelona Spain*, 2012. 9

[37] I. B. Hirsch, D. Armstrong, R. M. Bergenstal, B. Buckingham, B. P. Childs, W. L. Clarke, A. Peters, and H. Wolpert. Clinical application of emerging sensor technologies in diabetes management: consensus guidelines for continuous glucose monitoring (CGM). *Diabetes Technol Ther*, 10(4):232–44; quiz 245–6, 2008. 9, 30

[38] D. C. Klonoff, B. Buckingham, J. S. Christiansen, V. M. Montori, W. V. Tamborlane, R. A. Vigersky, and H. Wolpert. Continuous glucose monitoring: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*, 96(10):2968–79, 2011. 9

[39] J. H. DeVries. Continuous glucose monitoring - coming of age. *Eur J Endocrinol*, 166(1):1–4, 2012. 9

[40] E. S. Huang, M. O'Grady, A. Basu, A. Winn, P. John, J. Lee, D. Meltzer, C. Kollman, L. Laffel, W. Tamborlane, S. Weinzimer, T. Wysocki, and Continuous Juvenile Diabet Res Fdn. The cost-effectiveness of continuous glucose monitoring in type 1 diabetes. *Diabetes Care*, 33(6):1269–74, 2010. 9

[41] J. Halford and C. Harris. Determining clinical and psychological benefits and barriers with continuous glucose monitoring therapy. *Diabetes Technol Ther*, 12(3):201–5, 2010. 9, 10, 134

[42] M. Tansey, L. Laffel, J. Cheng, R. Beck, J. Coffey, E. Huang, C. Kollman, J. Lawrence, J. Lee, K. Ruedy, W. Tamborlane, T. Wysocki, and D. Xing. Satisfaction with continuous glucose monitoring in adults and youths with type 1 diabetes. *Diabet Med*, 28(9):1118–22, 2011. 10, 160, 162

[43] B. P. Kovatchev, D. Shields, and M. Breton. Graphical and numerical evaluation of continuous glucose sensing time lag. *Diabetes Technol Ther*, 11(3):139–43, 2009. 10

[44] B. A. Buckingham, C. Kollman, R. Beck, A. Kalajian, R. Fiallo-Scharer, M. J. Tansey, L. A. Fox, D. M. Wilson, S. A. Weinzimer, K. J. Ruedy, and W. V. Tamborlane. Evaluation of factors affecting CGMS calibration. *Diabetes Technol Ther*, 8(3):318–25, 2006. 10, 134

[45] Burdick J Kalajian A Kollman C Choy M Wilson DM Chase P; Diabetes Research in Children Network. Buckingham B, Block J. Response to nocturnal alarms using a real-time glucose sensor. *Diabetes Technol Ther*, 7(3):440–7, 2005. 11, 30

[46] B. Buckingham, D. M. Wilson, T. Lecher, R. Hanas, K. Kaiserman, and F. Cameron. Duration of nocturnal hypoglycemia before seizures. *Diabetes Care*, 31(11):2110–2, 2008. 11, 30

[47] A. Ceriello, M. A. Ihnat, and J. E. Thorpe. The "metabolic memory": Is more than just tight glucose control necessary to prevent diabetic complications? *J Clin Endocrinol Metab*, 94(2):410–5, 2009. 11

[48] C. Weber and O. Schnell. The assessment of glycemic variability and its impact on diabetes-related complications: an overview. *Diabetes Technol Ther*, 11(10):623–33, 2009. 11, 51, 55, 78

[49] M. J. Sheetz and G. L. King. Molecular understanding of hyperglycemia's adverse effects for diabetic complications. *JAMA*, 288(20):2579–88, 2002. 11, 52

[50] D Nathan, S Genuth, J Lachin, P Cleary, O Crofford, M Davis, L Rand, and C Siebert. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. the Diabetes Control and Complications Trial Research Group. *N Engl J Med*, 329(14):977–86, 1993. 12, 28

[51] I. H. de Boer, W. Sun, P. A. Cleary, J. M. Lachin, M. E. Molitch, M. W. Steffes, and B. Zinman. Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. *N Engl J Med*, 365(25):2366–76, 2011. 12

[52] N. H. White, W. Sun, P. A. Cleary, R. P. Danis, M. D. Davis, D. P. Hainsworth, L. D. Hubbard, J. M. Lachin, and D. M. Nathan. Prolonged effect of intensive therapy on the risk of retinopathy complications in patients with type 1 diabetes mellitus: 10 years after the Diabetes Control and Complications Trial. *Arch Ophthalmol*, 126(12):1707–15, 2008. 12

[53] D. M. Nathan, P. A. Cleary, J. Y. Backlund, S. M. Genuth, J. M. Lachin, T. J. Orchard, P. Raskin, and B. Zinman. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*, 353(25):2643–53, 2005. 12

[54] J. Q. Purnell, J. E. Hokanson, S. M. Marcovina, M. W. Steffes, P. A. Cleary, and J. D. Brunzell. Effect of excessive weight gain with intensive therapy of type 1 diabetes on lipid levels and blood pressure: results from the DCCT. *JAMA*, 280(2):140–6, 1998. 12, 107

[55] J. C. Pickup. Insulin-pump therapy for type 1 diabetes mellitus. *N Engl J Med*, 366(17):1616–24, Apr 2012. 12, 30, 161

[56] H. Anhalt and N. J. V. Bohannon. Insulin patch pumps: Their development and future in closed-loop systems. *Diabetes Technol Ther*, 12:S51–S58, 2010. 13

[57] E. Cummins, P. Royle, A. Snaith, A. Greene, L. Robertson, L. McIntyre, and N. Waugh. Clinical effectiveness and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes: systematic review and economic evaluation. *Health Technol Assess*, 14(11):iii–iv, xi–xvi, 1–181, 2010. 13

[58] J. C. Pickup and A. J. Sutton. Severe hypoglycaemia and glycaemic control in type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. *Diabet Med*, 25(7):765–74, 2008. 13

[59] M. Gimenez, M. Lara, and I. Conget. Sustained efficacy of continuous subcutaneous insulin infusion in type 1 diabetes subjects with recurrent non-severe and severe hypoglycemia and hypoglycemia unawareness: A pilot study. *Diabetes Technol Ther*, 12(7):517–21, 2010. 13

[60] J. C. Pickup. Are insulin pumps underutilized in type 1 diabetes? yes. *Diabetes Care*, 29(6):1449–52, 2006. 13

[61] E. Renard. Insulin pump use in Europe. *Diabetes Technol Ther*, 12:S29–S32, 2010. 13

[62] J. C. Pickup and P. Hammond. NICE guidance on continuous subcutaneous insulin infusion 2008: review of the technology appraisal guidance. *Diabet Med*, 26(1):1–4, 2009. 13

[63] S. A. White, J. A. Shaw, and D. E. Sutherland. Pancreas transplantation. *Lancet*, 373(9677):1808–17, 2009. 13

[64] A. M. J. Shapiro, C. Ricordi, B. J. Hering, H. Auchincloss, R. Lindblad, P. Robertson, A. Secchi, M. D. Brendel, T. Berney, D. C. Brennan, E. Cagliero, R. Alejandro, E. A. Ryan, B. DiMercurio, P. Morel, K. S. Polonsky, J. A. Reems, R. G. Bretzel, F. Bertuzzi, T. Froud, R. Kandaswamy, D. E. R. Sutherland, G. Eisenbarth, M. Segal, J. Preiksaitis, G. S. Korbutt, F. B. Barton, L. Viviano, V. Seyfert-Margolis, J. Bluestone, and J. R. T. Lakey. International trial of the Edmonton protocol for islet transplantation. *New Engl J Med*, 355(13):1318–30, 2006. 14

[65] E. A. Ryan, B. W. Paty, P. A. Senior, D. Bigam, E. Alfadhli, N. M. Kneteman, J. R. T. Lakey, and A. M. J. Shapir. Five-year follow-up after clinical islet transplantation. *Diabetes*, 54(7):2060–9, 2005. 14

[66] J. E. Tooley, F. Waldron-Lynch, and K. C. Herold. New and future immunomodulatory therapy in type 1 diabetes. *Trends Mol Med*, 2012. 14

[67] L. Heinemann. Variability of insulin absorption and insulin action. *Diabetes Technol Ther*, 4(5):673–82, 2002. 14, 159

[68] G. Sindelka, L. Heinemann, M. Berger, W. Frenck, and E. Chantelau. Effect of insulin concentration, subcutaneous fat thickness and skin temperature on subcutaneous insulin absoprtion in healthy subjects. *Diabetologia*, 37(4):377–80, 1994. 14, 15

[69] Kaastrup P Stallknecht B. Clausen, TS. Effect of insulin catheter wear-time on subcutaneous adipose tissue blood flow and insulin absorption in humans. *Diabetes Technol Ther*, 11(9):575–80, 2009. 14

[70] K. L. Swan, J. D. Dziura, G. M. Steil, G. R. Voskanyan, K. A. Sikes, A. T. Steffen, M. L. Martin, W. V. Tamborlane, and S. A. Weinzimer. Effect of age of infusion site and type of rapid-acting analog on pharmacodynamic parameters of

insulin boluses in youth with type 1 diabetes receiving insulin pump therapy. *Diabetes Care*, 32(2):240–4, 2009. 14

[71] S. Steiner, M. Hompesch, R. Pohl, P. Simms, F. Flacke, T. Mohr, A. Pfutzner, and L. Heinemann. A novel insulin formulation with a more rapid onset of action. *Diabetologia*, 51(9):1602–6, 2008. 15

[72] M. Hompesch, D. B. Muchmore, L. Morrow, and D. E. Vaughn. Accelerated insulin pharmacokinetics and improved postprandial glycemic control in patients with type 1 diabetes after coadministration of prandial insulins with hyaluronidase. *Diabetes Care*, 34(3):666–8, 2011. 15

[73] I. Raz, R. Weiss, Y. Yegorchikov, G. Bitton, R. Nagar, and B. Pesach. Effect of a local heating device on insulin and glucose pharmacokinetic profiles in an open-label, randomized, two-period, one-way crossover study in patients with type 1 diabetes using continuous subcutaneous insulin infusion. *Clin Ther*, 31(5):980–7, 2009. 15

[74] C. Weyer, A. Gottlieb, D. D. Kim, K. Lutz, S. Schwartz, M. Gutierrez, Y. Wang, J. A. Ruggles, O. G. Kolterman, and D. G. Maggs. Pramlintide reduces postprandial glucose excursions when added to regular insulin or insulin lispro in subjects with type 1 diabetes: a dose-timing study. *Diabetes Care*, 26(11):3074–9, 2003. 15

[75] A. Liebl, R. Hoogma, E. Renard, P. H. Geelhoed-Duijvestijn, E. Klein, J. Diglas, L. Kessler, V. Melki, P. Diem, J. M. Brun, P. Schaepelynck-Belicar, and T. Frei. A reduction in severe hypoglycaemia in type 1 diabetes in a randomized crossover study of continuous intraperitoneal compared with subcutaneous insulin infusion. *Diabetes Obes Metab*, 11(11):1001–8, 2009. 16

[76] H. Gin, E. Renard, V. Melki, S. Boivin, P. Schaepelynck-Belicar, B. Guerci, J. L. Selam, J. M. Brun, J. P. Riveline, B. Estour, B. Catargi, and Evadiac Study Grp. Combined improvements in implantable pump technology and insulin stability allow safe and effective long term intraperitoneal insulin delivery in type 1 diabetic patients: the EVADIAC experience. *Diabetes Metab*, 29(6):602–7, 2003. 16

[77] K. Rave, E. Potocka, L. Heinemann, T. Heise, A. H. Boss, M. Marino, D. Costello, and R. Chen. Pharmacokinetics and linear exposure of AFRESA compared

with the subcutaneous injection of regular human insulin. *Diabetes Obes Metab*, 11(7):715–20, 2009. 16

[78] J. Rosenstock, R. Bergenstal, R. A. DeFronzo, I. B. Hirsch, D. Klonoff, A. H. Boss, D. Kramer, R. Petrucci, W. Yu, B. Levy, and Grp Study. Efficacy and safety of Technosphere inhaled insulin compared with Technosphere powder placebo in insulin-naive type 2 diabetes suboptimally controlled with oral agents. *Diabetes Care*, 31(11):2177–82, 2008. 16

[79] R. J. Pettis, L. Hirsch, C. Kapitza, L. Nosek, U. Hovelmann, H. J. Kurth, D. E. Sutter, N. G. Harvey, and L. Heinemann. Microneedle-based intradermal versus subcutaneous administration of regular human insulin or insulin lispro: pharmacokinetics and postprandial glycemic excursions in patients with type 1 diabetes. *Diabetes Technol Ther*, 13(4):443–50, 2011. 16

[80] K. Kumareswaran, M. L. Evans, and R. Hovorka. Closed-loop insulin delivery: towards improved diabetes care. *Discov Med*, 13(69):159–70, 2012. 17, 21

[81] R. Hovorka, V. Canonico, L. J. Chassin, U. Haueter, M. Massi-Benedetti, M. Orsini Federici, T. R. Pieber, H. C. Schaller, L. Schaupp, T. Vering, and M. E. Wilinska. Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes. *Physiol Meas*, 25(4):905–20, 2004. 18, 34, 51

[82] G. M. Steil, A. E. Panteleon, and K. Rebrin. Closed-loop insulin delivery-the path to physiological glucose control. *Adv Drug Deliv Rev*, 56(2):125–44, 2004. 18

[83] J. R. Castle, J. M. Engle, J. E. L. Youssef, R. G. Massoud, K. C. J. Yuen, R. Kagan, and W. K. Ward. Novel use of glucagon in a closed-loop system for prevention of hypoglycemia in type 1 diabetes. *Diabetes Care*, 33(6):1282–7, 2010. 18, 22, 25, 153, 155

[84] J. El Youssef, J. R. Castle, D. L. Branigan, R. G. Massoud, M. E. Breen, P. G. Jacobs, B. W. Bequette, and W. K. Ward. A controlled study of the effectiveness of an adaptive closed-loop algorithm to minimize corticosteroid-induced stress hyperglycemia in type 1 diabetes. *J Diabetes Sci Technol*, 5(6):1312–26, 2011. 18, 22, 153

[85] G. M. Steil, C. C. Palerm, N. Kurtz, G. Voskanyan, A. Roy, S. Paz, and F. R.

Kandeel. The effect of insulin feedback on closed loop glucose control. *J Clin Endocrinol Metab*, 96(5):1402–8, 2011. 18, 22, 24, 153

[86] AH Kadish. Automation control of blood sugar.I. Servomechanism for glucose monitoring and control. *Am J Med Electron*, 3(2):82–6, 1964. 19

[87] A. M. Albisser, B. S. Leibel, T. G. Ewart, Davidova.Z, C. K. Botz, and W. Zingg. Artificial endocrine pancreas. *Diabetes*, 23(5):389–96, 1974. 19

[88] E. F. Pfeiffer, C. Thum, and A. H. Clemens. Artificial beta cell - continuous control of blood-sugar by external regulation of insulin infusion. *Horm Metab Res*, 6(5):339–42, 1974. 19

[89] A. H. Clemens, P. H. Chang, and R. W. Myers. The development of Biostator, a glucose controlled insulin infusion system (GCIIS). *Horm Metab Res*, Suppl 7:23–33, 1977. 19

[90] R. Hovorka, L. J. Chassin, M. E. Wilinska, V. Canonico, J. A. Akwi, M. O. Federici, M. Massi-Benedetti, I. Hutzli, C. Zaugg, H. Kaufmann, M. Both, T. Vering, H. C. Schaller, L. Schaupp, M. Bodenlenz, and T. R. Pieber. Closing the loop: the ADICOL experience. *Diabetes Technol Ther*, 6(3):307–18, 2004. 19

[91] G. M. Steil, K. Rebrin, C. Darwin, F. Hariri, and M. F. Saad. Feasibility of automating insulin delivery for the treatment of type 1 diabetes. *Diabetes*, 55(12):3344–50, 2006. 19, 22, 24

[92] P Galley, R Wagner, H Buck, S Weinert, S Bousamra, J Long, A Thukral, D Kenyon, G Freckmann, N Jendrike, C Haug, and A Abicht. Use of subcutaneous continuous glucose measurements to drive real-time algorithm-directed insulin infusion recommendations. *Diabetes Technol Ther*, 6:245–6, 2004. 19

[93] R. Hovorka. Closed-loop insulin delivery: from bench to clinical practice. *Nat Rev Endocrinol*, 7(7):385–95, 2011. 20, 56, 159

[94] NICE. Management of diabetes from preconception to the postnatal period: summary of NICE guidance. *BMJ*, 336(7646):714–7, 2008. 20, 86, 93, 106, 116, 121, 128

[95] American Diabetes Association. Postprandial blood glucose. *Diabetes Care*, 24(4):775–8, 2001. 20, 55

[96] D. Rodbard. Interpretation of continuous glucose monitoring data: glycemic variability and quality of glycemic control. *Diabetes Technol Ther*, 11 Suppl 1:S55–67, 2009. 20

[97] BP Kovatchev, DJ Cox, LA Gonder-Frederick, D Young-Hyman, D Schlundt, and W Clarke. Assessment of risk for severe hypoglycemia among adults with IDDM: validation of the low blood glucose index. *Diabetes Care*, 21(11):1870–5, 1998. 20, 36, 121

[98] D. B. Keenan, B. Grosman, H. W. Clark, A. Roy, S. A. Weinzimer, R. V. Shah, and J. J. Mastrototaro. Continuous glucose monitoring considerations for the development of a closed-loop artificial pancreas system. *J Diabetes Sci Technol*, 5(6):1327–36, 2011. 20

[99] P. Choudhary, J. Shin, Y. Wang, M. L. Evans, P. J. Hammond, D. Kerr, J. A. Shaw, J. C. Pickup, and S. A. Amiel. Insulin pump therapy with automated insulin suspension in response to hypoglycemia: Reduction in nocturnal hypoglycemia in those at greatest risk. *Diabetes Care*, 34(9):2023–5, 2011. 21, 22

[100] T. Danne, O. Kordonouri, M. Holder, H. Haberland, S. Golembowski, K. Remus, S. Blasig, T. Wadien, S. Zierow, R. Hartmann, and A. Thomas. Prevention of hypoglycemia by using low glucose suspend function in sensor-augmented pump therapy. *Diabetes Technol Ther*, 13(11):1129–34, 2011. 21, 22

[101] B. Buckingham, H. P. Chase, E. Dassau, E. Cobry, P. Clinton, V. Gage, K. Caswell, J. Wilkinson, F. Cameron, H. Lee, B. W. Bequette, and F. J. Doyle. Prevention of nocturnal hypoglycemia using predictive alarm algorithms and insulin pump suspension. *Diabetes Care*, 33(5):1013–7, 2010. 21, 22, 23, 153

[102] B. Buckingham, E. Cobry, P. Clinton, V. Gage, K. Caswell, E. Kunselman, F. Cameron, and H. P. Chase. Preventing hypoglycemia using predictive alarm algorithms and insulin pump suspension. *Diabetes Technol Ther*, 11(2):93–7, 2009. 21, 22, 23

[103] R. Hovorka, K. Kumareswaran, J. Harris, J. M. Allen, D. Elleri, D. Xing, C. Kollman, M. Nodale, H. R. Murphy, D. B. Dunger, S. A. Amiel, S. R. Heller, M. E. Wilinska, and M. L. Evans. Overnight closed loop insulin delivery (artificial pancreas) in adults with type 1 diabetes: crossover randomised controlled studies. *BMJ*, 342:d1855, 2011. 22

[104] R. Hovorka, J. M. Allen, D. Elleri, L. J. Chassin, J. Harris, D. Y. Xing, C. Kollman, T. Hovorka, A. M. F. Larsen, M. Nodale, A. De Palma, M. E. Wilinska, C. L. Acerini, and D. B. Dunger. Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. *Lancet*, 375(9716):743–51, 2010. 22, 23, 30, 36, 62, 110

[105] B. Kovatchev, C. Cobelli, E. Renard, S. Anderson, M. Breton, S. Patek, W. Clarke, D. Bruttomesso, A. Maran, S. Costa, A. Avogaro, C. Dalla Man, A. Facchinetti, L. Magni, G. De Nicolao, J. Place, and A. Farret. Multinational study of subcutaneous model-predictive closed-loop control in type 1 diabetes mellitus: summary of the results. *J Diabetes Sci Technol*, 4(6):1374–81, 2010. 22, 23, 153, 154, 155

[106] D. Elleri, J. M. Allen, M. Nodale, M. E. Wilinska, J. S. Mangat, A. M. Larsen, C. L. Acerini, D. B. Dunger, and R. Hovorka. Automated overnight closed-loop glucose control in young children with type 1 diabetes. *Diabetes Technol Ther*, 13(4):419–24, 2011. 22, 23, 154, 156, 161

[107] D Elleri, JM Allen, K Kumareswaran, L Leelarathna, M Nodale, K Caldwell, H Murphy, ME Wilinska, CL Acerini, DB Dunger, and R Hovorka. Day-and-night closed-loop glucose control in adolescents with type 1 diabetes. *Diabetes*, 60(Suppl 1):A41–A41, 2011. 22, 24

[108] H. R. Murphy, D. Elleri, J. M. Allen, J. Harris, D. Simmons, G. Rayman, R. Temple, D. B. Dunger, A. Haidar, M. Nodale, M. E. Wilinska, and R. Hovorka. Closed-loop insulin delivery during pregnancy complicated by type 1 diabetes. *Diabetes Care*, 34(2):406–11, 2011. 22, 24, 88, 89, 93, 105, 107, 108, 135, 144

[109] H. R. Murphy, K. Kumareswaran, D. Elleri, J. M. Allen, K. Caldwell, M. Biagioni, D. Simmons, D. B. Dunger, M. Nodale, M. E. Wilinska, S. A. Amiel, and R. Hovorka. Safety and efficacy of 24-h closed-loop insulin delivery in well-controlled pregnant women with type 1 diabetes: a randomized crossover case series. *Diabetes Care*, 34(12):2527–9, 2011. 22

[110] E. Atlas, R. Nimri, S. Miller, E. A. Grunberg, and M. Phillip. MD-logic artificial pancreas system: a pilot study in adults with type 1 diabetes. *Diabetes Care*, 33(5):1072–6, 2010. 22, 25

[111] S. A. Weinzimer, G. M. Steil, K. L. Swan, J. Dziura, N. Kurtz, and W. V. Tamborlane. Fully automated closed-loop insulin delivery versus semiautomated

hybrid control in pediatric patients with type 1 diabetes using an artificial pancreas. *Diabetes Care*, 31(5):934–9, 2008. 22, 24, 153

[112] F. H. El-Khatib, S. J. Russell, D. M. Nathan, R. G. Sutherlin, and E. R. Damiano. A bihormonal closed-loop artificial pancreas for type 1 diabetes. *Sci Transl Med*, 2(27):27ra27, 2010. 22, 25, 153

[113] E. Renard, J. Place, M. Cantwell, H. Chevassus, and C. C. Palerm. Closed-loop insulin delivery using a subcutaneous glucose sensor and intraperitoneal insulin delivery feasibility study testing a new model for the artificial pancreas. *Diabetes Care*, 33(1):121–7, 2010. 22, 26

[114] P. Agrawal, J. B. Welsh, B. Kannard, S. Askari, Q. Yang, and F. R. Kaufman. Usage and effectiveness of the low glucose suspend feature of the Medtronic Paradigm Veo insulin pump. *J Diabetes Sci Technol*, 5(5):1137–41, 2011. 21

[115] S. Garg, R. L. Brazg, T. S. Bailey, B. A. Buckingham, R. H. Slover, D. C. Klonoff, J. Shin, J. B. Welsh, and F. R. Kaufman. Reduction in duration of hypoglycemia by automatic suspension of insulin delivery: The in-clinic ASPIRE study. *Diabetes Technol Ther*, 14(3):205–9, 2012. 21

[116] R. P. Radermecker and A. J. Scheen. Continuous subcutaneous insulin infusion with short-acting insulin analogues or human regular insulin: efficacy, safety, quality of life, and cost-effectiveness. *Diabetes Metab Res Rev*, 20(3):178–88, 2004. 23

[117] D. Elleri, J. M. Allen, M. Nodale, M. E. Wilinska, C. L. Acerini, D. B. Dunger, and R. Hovorka. Suspended insulin infusion during overnight closed-loop glucose control in children and adolescents with type 1 diabetes. *Diabet Med*, 27(4):480–4, 2010. 23

[118] E. Cengiz, K. L. Swan, W. V. Tamborlane, G. M. Steil, A. T. Steffen, and S. A. Weinzimer. Is an automatic pump suspension feature safe for children with type 1 diabetes? An exploratory analysis with a closed-loop system. *Diabetes Technol Ther*, 11(4):207–10, 2009. 23

[119] D. M. Nathan and others. The DCCT Research Group. Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. *Am J Med*, 90(4):450–9, 1991. 23, 28, 29, 30, 51, 85

[120] K. Kumareswaran, D. Elleri, J. M. Allen, J. Harris, D. Xing, C. Kollman, M. Nodale, H. R. Murphy, S. A. Amiel, S. R. Heller, M. E. Wilinska, C. L. Acerini, M. L. Evans, D. B. Dunger, and R. Hovorka. Meta-analysis of overnight closed-loop randomized studies in children and adults with type 1 diabetes: the Cambridge cohort. *J Diabetes Sci Technol*, 5(6):1352–62, 2011. 23, 151

[121] SA Weinzimer, JL Sherr, E Cengiz, G Kim, L Carria, and W Tamborlane. Effect of adjuvant injected pramlintide on closed-loop automated insulin delivery. *Diabetes*, 60(Suppl 1):A253–A253, 2011. 24

[122] W. K. Ward, J. R. Castle, and J. El Youssef. Safe glycemic management during closed-loop treatment of type 1 diabetes: the role of glucagon, use of multiple sensors, and compensation for stress hyperglycemia. *J Diabetes Sci Technol*, 5(6):1373–80, 2011. 25

[123] E. Renard, G. Costalat, H. Chevassus, and J. Bringer. Closed loop insulin delivery using implanted insulin pumps and sensors in type 1 diabetic patients. *Diabetes Res Clin Pract*, 74:S173–7, 2006. 26

[124] M. E. Wilinska, L. J. Chassin, C. L. Acerini, J. M. Allen, D. B. Dunger, and R. Hovorka. Simulation environment to evaluate closed-loop insulin delivery systems in type 1 diabetes. *J Diabetes Sci Technol*, 4(1):132–44, 2010. 26

[125] Man CD Cobelli C. Kovatchev BP, Breton M. In silico preclinical trials: a proof of concept in closed-loop control of type 1 diabetes. *J Diabetes Sci Technol*, 3(1):43–55, 2009. 26

[126] D. Wild, R. von Maltzahn, E. Brohan, T. Christensen, P. Clauson, and L. Gonder-Frederick. A critical review of the literature on fear of hypoglycemia in diabetes: Implications for diabetes management and patient education. *Patient Educ Couns*, 68(1):10–5, 2007. 28, 132

[127] R. Nixon and J. C. Pickup. Fear of hypoglycemia in type 1 diabetes managed by continuous subcutaneous insulin infusion: is it associated with poor glycemic control? *Diabetes Technol Ther*, 13(2):93–8, 2011. 28

[128] Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association workgroup on hypoglycemia. *Diabetes Care*, 28(5):1245–9, 2005. 28

[129] K. M. MacLeod, D. A. Hepburn, and B. M. Frier. Frequency and morbidity of severe hypoglycaemia in insulin-treated diabetic patients. *Diabet Med*, 10(3):238–45, 1993. 28, 29

[130] P. E. Cryer, S. N. Davis, and H. Shamoon. Hypoglycemia in diabetes. *Diabetes Care*, 26(6):1902–12, 2003. 29, 52

[131] P. E. Cryer. Current concepts: Diverse causes of hypoglycemia-associated autonomic failure in diabetes. *New Engl J Med*, 350(22):2272–9, 2004. 29

[132] T. W. Jones, P. Porter, R. S. Sherwin, E. A. Davis, P. O'Leary, F. Frazer, G. Byrne, S. Stick, and W. V. Tamborlane. Decreased epinephrine responses to hypoglycemia during sleep. *N Engl J Med*, 338(23):1657–62, 1998. 29

[133] S. Banarer and P. E. Cryer. Sleep-related hypoglycemia-associated autonomic failure in type 1 diabetes: reduced awakening from sleep during hypoglycemia. *Diabetes*, 52(5):1195–203, 2003. 29

[134] T. T. Ly, T. W. Jones, A. Griffiths, J. Dart, E. A. Davis, S. Stick, and A. Wilson. Hypoglycemia does not change the threshold for arousal from sleep in adolescents with type 1 diabetes. *Diabetes Technol Ther*, 14(2):101–4, 2012. 29

[135] Juvenile Diabetes Research Foundation CGM Study Group. Prolonged nocturnal hypoglycemia is common during 12 months of continuous glucose monitoring in children and adults with type 1 diabetes. *Diabetes Care*, 33(5):1004–8, 2010. 29

[136] G. Gill, A. Woodward, I. Casson, and P. Weston. Cardiac arrhythmia and nocturnal hypoglycaemia in type 1 diabetes-the 'dead in bed' syndrome revisited. *Diabetologia*, 52(1):42–45, 2009. 29

[137] I. Campbell. Dead in bed syndrome: a new manifestation of nocturnal hypoglycaemia? *Diabet Med*, 8(1):3–4, 1991. 29

[138] A. M. Secrest, D. J. Becker, S. F. Kelsey, R. E. Laporte, and T. J. Orchard. Characterizing sudden death and dead-in-bed syndrome in type 1 diabetes: analysis from two childhood-onset type 1 diabetes registries. *Diabet Med*, 28(3):293–300, 2011. 29

[139] P. King, M. F. Kong, H. Parkin, I. A. Macdonald, and R. B. Tattersall. Well-being, cerebral function, and physical fatigue after nocturnal hypoglycemia in IDDM. *Diabetes Care*, 21(3):341–5, 1998. 30

[140] B. O. Asvold, T. Sand, K. Hestad, and M. R. Bjorgaas. Cognitive function in type 1 diabetic adults with early exposure to severe hypoglycemia: a 16-year follow-up study. *Diabetes Care*, 33(9):1945–7, 2010. 30

[141] S Genuth and DCCT Research Group. Long-term effect of diabetes and its treatment on cognitive function. *New Engl J Med*, 356(18):1842–52, 2007. 30

[142] M. F. Carroll and D. S. Schade. The dawn phenomenon revisited: implications for diabetes therapy. *Endocr Pract*, 11(1):55–64, 2005. 51, 79

[143] A. Vella, P. Shah, A. Basu, and R. A. Rizza. Prandial insulin and the systemic appearance of meal-derived glucose in people with type 1 diabetes. *Diabetes Care*, 31(11):2230–1, 2008. 55

[144] M. S. Rendell and L. Jovanovic. Targeting postprandial hyperglycemia. *Metabolism*, 55(9):1263–81, 2006. 55, 108

[145] Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. *BMJ*, 325(7367):746, 2002. 55

[146] D. J. Jenkins, T. M. Wolever, R. H. Taylor, H. Barker, H. Fielden, J. M. Baldwin, A. C. Bowling, H. C. Newman, A. L. Jenkins, and D. V. Goff. Glycemic index of foods: a physiological basis for carbohydrate exchange. *Am J Clin Nutr*, 34(3):362–6, 1981. 55

[147] M. Parillo, G. Annuzzi, A. A. Rivellese, L. Bozzetto, R. Alessandrini, G. Riccardi, and B. Capaldo. Effects of meals with different glycaemic index on postprandial blood glucose response in patients with type 1 diabetes treated with continuous subcutaneous insulin infusion. *Diabet Med*, 28(2):227–9, 2011. 56

[148] J. Brand-Miller, S. Hayne, P. Petocz, and S. Colagiuri. Low-glycemic index diets in the management of diabetes: a meta-analysis of randomized controlled trials. *Diabetes Care*, 26(8):2261–7, 2003. 56

[149] A. L. Olinder, A. Kernell, and B. Smide. Missed bolus doses: devastating for metabolic control in CSII-treated adolescents with type 1 diabetes. *Pediatr Diabetes*, 10(2):142–8, 2009. 56

[150] Y. M. Luijf, A. C. van Bon, J. B. Hoekstra, and J. H. Devries. Premeal injection of rapid-acting insulin reduces postprandial glycemic excursions in type 1 diabetes. *Diabetes Care*, 33(10):2152–5, 2010. 56, 78

[151] E. Cobry, K. McFann, L. Messer, V. Gage, B. VanderWel, L. Horton, and H. P. Chase. Timing of meal insulin boluses to achieve optimal postprandial glycemic control in patients with type 1 diabetes. *Diabetes Technol Ther*, 12(3):173–7, 2010. 56, 78

[152] J. C. Brand-Miller, K. Fatema, C. Middlemiss, M. Bare, V. Liu, F. Atkinson, and P. Petocz. Effect of alcoholic beverages on postprandial glycemia and insulinemia in lean, young, healthy adults. *Am J Clin Nutr*, 85(6):1545–51, 2007. 56

[153] L. L. Koppes, J. M. Dekker, H. F. Hendriks, L. M. Bouter, and R. J. Heine. Moderate alcohol consumption lowers the risk of type 2 diabetes: a meta-analysis of prospective observational studies. *Diabetes Care*, 28(3):719–25, 2005. 56

[154] J. W. Beulens, J. S. Kruidhof, D. E. Grobbee, N. Chaturvedi, J. H. Fuller, and S. S. Soedamah-Muthu. Alcohol consumption and risk of microvascular complications in type 1 diabetes patients: the EURODIAB Prospective Complications Study. *Diabetologia*, 51(9):1631–8, 2008. 56

[155] D. R. Meeking and D. A. Cavan. Alcohol ingestion and glycaemic control in patients with insulin-dependent diabetes mellitus. *Diabet Med*, 14(4):279–83, 1997. 56, 58

[156] T. Richardson, M. Weiss, P. Thomas, and D. Kerr. Day after the night before: influence of evening alcohol on risk of hypoglycemia in patients with type 1 diabetes. *Diabetes Care*, 28(7):1801–2, 2005. 57

[157] D. Kerr, E. Cheyne, P. Thomas, and R. Sherwin. Influence of acute alcohol ingestion on the hormonal responses to modest hypoglycaemia in patients with type 1 diabetes. *Diabet Med*, 24(3):312–6, 2007. 57

[158] B. C. Turner, E. Jenkins, D. Kerr, R. S. Sherwin, and D. A. Cavan. The effect of evening alcohol consumption on next-morning glucose control in type 1 diabetes. *Diabetes Care*, 24(11):1888–93, 2001. 57, 60, 78

[159] E. H. Cheyne, R. S. Sherwin, M. J. Lunt, D. A. Cavan, P. W. Thomas, and D. Kerr. Influence of alcohol on cognitive performance during mild hypoglycaemia; implications for type 1 diabetes. *Diabet Med*, 21(3):230–7, 2004. 57

[160] D. Kerr, I. A. Macdonald, S. R. Heller, and R. B. Tattersall. Alcohol causes hypoglycemic unawareness in healthy volunteers and patients with type 1 (insulin-dependent) diabetes. *Diabetologia*, 33(4):216–221, 1990. 57

[161] G. T. Passananti, C. A. Wolff, and E. S. Vesell. Reproducibility of individual rates of ethanol metabolism in fasting subjects. *Clin Pharmacol Ther*, 47(3):389–96, 1990. 58, 79

[162] A. G. Fraser, S. B. Rosalki, G. D. Gamble, and R. E. Pounder. Inter-individual and intra-individual variability of ethanol concentration-time profiles: comparsion of ethanol ingestion before or after an evening meal. *Br J Clin Pharmacol*, 40(4):387–92, 1995. 58, 78, 79

[163] N. Ramchandani, J. M. Cantey-Kiser, C. A. Alter, S. J. Brink, S. D. Yeager, W. V. Tamborlane, and S. R. Chipkin. Self-reported factors that affect glycemic control in college students with type 1 diabetes. *Diabetes Educ*, 26(4):656–66, 2000. 58

[164] USDA. USDA National Nutrient Database for Standard Reference. Technical Report 7 Dec, 2011. 72

[165] S. Kalhan, K. Rossi, L. Gruca, E. Burkett, and A. O'Brien. Glucose turnover and gluconeogenesis in human pregnancy. *J Clin Invest*, 100(7):1775–81, 1997. 81

[166] H. R. Murphy, J. M. Roland, T. C. Skinner, D. Simmons, E. Gurnell, N. J. Morrish, S. C. Soo, S. Kelly, B. Lim, J. Randall, S. Thompsett, and R. C. Temple. Effectiveness of a regional prepregnancy care program in women with type 1 and type 2 diabetes: benefits beyond glycemic control. *Diabetes Care*, 33(12):2514–20, 2010. 81

[167] I.M. Evers, H.W. De Valk, and G.H.A. Visser. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. *BMJ*, 328(7445):915, 2004. 81, 83

[168] R. C. Temple, V. J. Aldridge, and H. R. Murphy. Prepregnancy care and pregnancy outcomes in women with type 1 diabetes. *Diabetes Care*, 29(8):1744–9, 2006. 81

[169] M. Persson, M. Norman, and U. Hanson. Obstetric and perinatal outcomes in type 1 diabetic pregnancies: A large, population-based study. *Diabetes Care*, 32(11):2005–9, 2009. 81, 82

[170] M. C. Macintosh, K. M. Fleming, J. A. Bailey, P. Doyle, J. Modder, D. Acolet, S. Golightly, and A. Miller. Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. *BMJ*, 333(7560):177, 2006. 81, 82

[171] M. U. Baumann, S. Deborde, and N. P. Illsley. Placental glucose transfer and fetal growth. *Endocrine*, 19(1):13–22, 2002. 81

[172] A. Kerssen, H. W. de Valk, and G. H. Visser. Increased second trimester maternal glucose levels are related to extremely large-for-gestational-age infants in women with type 1 diabetes. *Diabetes Care*, 30(5):1069–74, 2007. 82

[173] L. Herranz, L. F. Pallardo, N. Hillman, P. Martin-Vaquero, A. Villarroel, and A. Fernandez. Maternal third trimester hyperglycaemic excursions predict large-for-gestational-age infants in type 1 diabetic pregnancy. *Diabetes Res Clin Pract*, 75(1):42–6, 2007. 82

[174] M. C. Jolly, N. J. Sebire, J. P. Harris, L. Regan, and S. Robinson. Risk factors for macrosomia and its clinical consequences: a study of 350,311 pregnancies. *Eur J Obstet Gynecol Reprod Biol*, 111(1):9–14, 2003. 82

[175] Pregnancy outcomes in the Diabetes Control and Complications Trial. *Am J Obstet Gynecol*, 174(4):1343–53, 1996. 82, 86

[176] L. Ringholm, U. Pedersen-Bjergaard, B. Thorsteinsson, P. Damm, and E. R. Mathiesen. Hypoglycaemia during pregnancy in women with type 1 diabetes. *Diabet Med*, 29(5):558–66, 2012. 82, 83, 114, 161

[177] L. R. Nielsen, U. Pedersen-Bjergaard, B. Thorsteinsson, M. Johansen, P. Damm, and E. R. Mathiesen. Hypoglycemia in pregnant women with type 1 diabetes: predictors and role of metabolic control. *Diabetes Care*, 31(1):9–14, 2008. 82, 83, 128

[178] B. M. Rosenn, M. Miodovnik, J. C. Khoury, and T. A. Siddiqi. Counterregulatory hormonal responses to hypoglycemia during pregnancy. *Obstet Gynecol*, 87(4):568–74, 1996. 83

[179] P. J. Leinonen, V. K. Hiilesmaa, R. J. Kaaja, and K. A. Teramo. Maternal mortality in type 1 diabetes. *Diabetes Care*, 24(8):1501–2, 2001. 83

[180] I. W. Smoak and T. W. Sadler. Embryopathic effects of short-term exposure to hypoglycemia in mouse embryos in vitro. *Am J Obstet Gynecol*, 163(2):619–24, 1990. 83

[181] T. A. Buchanan, J. K. Schemmer, and N. Freinkel. Embryotoxic effects of brief maternal insulin-hypoglycemia during organogenesis in the rat. *J Clin Invest*, 78(3):643–9, 1986. 83

[182] E. W. ter Braak, I. M. Evers, D. Willem Erkelens, and G. H. Visser. Maternal hypoglycemia during pregnancy in type 1 diabetes: maternal and fetal consequences. *Diabetes Metab Res Rev*, 18(2):96–105, 2002. 83

[183] A. Garcia-Patterson, R. Corcoy, M. Balsells, O. Altirriba, J. M. Adelantado, L. Cabero, and A. de Leiva. In pregnancies with gestational diabetes mellitus and intensive therapy, perinatal outcome is worse in small-for-gestational-age newborns. *Am J Obstet Gynecol*, 179(2):481–5, 1998. 83

[184] E. Stenninger, R. Flink, B. Eriksson, and C. Sahlen. Long-term neurological dysfunction and neonatal hypoglycaemia after diabetic pregnancy. *Arch Dis Child Fetal Neonatal Ed*, 79(3):F174–9, 1998. 83

[185] A. Thorell, M. F. Hirshman, J. Nygren, L. Jorfeldt, J. F. Wojtaszewski, S. D. Dufresne, E. S. Horton, O. Ljungqvist, and L. J. Goodyear. Exercise and insulin cause GLUT-4 translocation in human skeletal muscle. *Am J Physiol*, 277(4 Pt 1):E733–41, 1999. 84

[186] P. E. Cryer. Exercise-related hypoglycemia-associated autonomic failure in diabetes. *Diabetes*, 58(9):1951–2, 2009. 84, 85

[187] A. C. Ertl and S. N. Davis. Evidence for a vicious cycle of exercise and hypoglycemia in type 1 diabetes mellitus. *Diabetes Metab Res Rev*, 20(2):124–30, 2004. 84, 110, 129, 132

[188] E. B. Marliss and M. Vranic. Intense exercise has unique effects on both insulin release and its roles in glucoregulation: implications for diabetes. *Diabetes*, 51 Suppl 1:S271–83, 2002. 84

[189] R. J. Sigal, C. Purdon, S. J. Fisher, J. B. Halter, M. Vranic, and E. B. Marliss. Hyperinsulinemia prevents prolonged hyperglycemia after intense exercise in insulin-dependent diabetic subjects. *J Clin Endocrinol Metab*, 79(4):1049–57, 1994. 84

[190] K. J. Guelfi, T. W. Jones, and P. A. Fournier. The decline in blood glucose levels is less with intermittent high-intensity compared with moderate exercise in individuals with type 1 diabetes. *Diabetes Care*, 28(6):1289–94, 2005. 85, 129

[191] V. A. Bussau, L. D. Ferreira, T. W. Jones, and P. A. Fournier. The 10-s maximal sprint: a novel approach to counter an exercise-mediated fall in glycemia in individuals with type 1 diabetes. *Diabetes Care*, 29(3):601–6, 2006. 85

[192] I. W. Gallen, C. Hume, and A. Lumb. Fuelling the athlete with type 1 diabetes. *Diabetes Obes Metab*, 13(2):130–6, 2011. 85, 86

[193] J. J. Ruegemer, R. W. Squires, H. M. Marsh, M. W. Haymond, P. E. Cryer, R. A. Rizza, and J. M. Miles. Differences between prebreakfast and late afternoon glycemic responses to exercise in IDDM patients. *Diabetes Care*, 13(2):104–10, 1990. 85

[194] S. K. McMahon, L. D. Ferreira, N. Ratnam, R. J. Davey, L. M. Youngs, E. A. Davis, P. A. Fournier, and T. W. Jones. Glucose requirements to maintain euglycemia after moderate-intensity afternoon exercise in adolescents with type 1 diabetes are increased in a biphasic manner. *J Clin Endocrinol Metab*, 92(3):963–8, 2007. 85, 110, 132

[195] M. J. Tansey, E. Tsalikian, R. W. Beck, N. Mauras, B. A. Buckingham, S. A. Weinzimer, K. F. Janz, C. Kollman, D. Xing, K. J. Ruedy, M. W. Steffes, T. M. Borland, R. J. Singh, and W. V. Tamborlane. The effects of aerobic exercise on glucose and counterregulatory hormone concentrations in children with type 1 diabetes. *Diabetes Care*, 29(1):20–5, 2006. 85, 110

[196] P. Galassetti, D. Tate, R. A. Neill, S. Morrey, D. H. Wasserman, and S. N. Davis. Effect of antecedent hypoglycemia on counterregulatory responses to subsequent euglycemic exercise in type 1 diabetes. *Diabetes*, 52(7):1761–9, 2003. 85, 110

[197] D. A. Sandoval, D. L. Guy, M. A. Richardson, A. C. Ertl, and S. N. Davis. Effects of low and moderate antecedent exercise on counterregulatory responses to subsequent hypoglycemia in type 1 diabetes. *Diabetes*, 53(7):1798–806, 2004. 85, 110

[198] E. J. Stevenson, C. Williams, L. E. Mash, B. Phillips, and M. L. Nute. Influence of high-carbohydrate mixed meals with different glycemic indexes on substrate utilization during subsequent exercise in women. *Am J Clin Nutr*, 84(2):354–60, 2006. 86

[199] R. Rabasa-Lhoret, J. Bourque, F. Ducros, and J. L. Chiasson. Guidelines for premeal insulin dose reduction for postprandial exercise of different intensities and durations in type 1 diabetic subjects treated intensively with a basal-bolus insulin regimen (ultralente-lispro). *Diabetes Care*, 24(4):625–30, 2001. 86

[200] E. Tsalikian, C. Kollman, W. B. Tamborlane, R. W. Beck, R. Fiallo-Scharer, L. Fox, K. F. Janz, K. J. Ruedy, D. Wilson, D. Xing, and S. A. Weinzimer. Prevention of hypoglycemia during exercise in children with type 1 diabetes by suspending basal insulin. *Diabetes Care*, 29(10):2200–4, 2006. 86

[201] C. E. Taplin, E. Cobry, L. Messer, K. McFann, H. P. Chase, and R. Fiallo-Scharer. Preventing post-exercise nocturnal hypoglycemia in children with type 1 diabetes. *J Pediatr*, 157(5):784–8 e1, 2010. 86

[202] J. H. Koeslag. Post-exercise ketosis and the hormone response to exercise: a review. *Med Sci Sports Exerc*, 14(5):327–34, 1982. 86

[203] R. M. Bracken, D. J. West, J. W. Stephens, L. P. Kilduff, S. Luzio, and S. C. Bain. Impact of pre-exercise rapid-acting insulin reductions on ketogenesis following running in type 1 diabetes. *Diabet Med*, 28(2):218–22, 2011. 86

[204] Z. Jankovec, M. Krcma, J. Gruberova, J. Komorousova, J. Tomesova, M. Zourek, and Z. Rusavy. Influence of physical activity on metabolic state within a 3-h interruption of continuous subcutaneous insulin infusion in patients with type 1 diabetes. *Diabetes Technol Ther*, 13(12):1234–9, 2011. 86

[205] J. C. Thow, A. B. Johnson, M. Antsiferov, and P. D. Home. Exercise augments the absorption of isophane (NPH) insulin. *Diabet Med*, 6(4):342–5, 1989. 86

[206] E. Ferrannini, B. Linde, and O. Faber. Effect of bicycle exercise on insulin absorption and subcutaneous blood flow in the normal subject. *Clin Physiol*, 2(1):59–70, 1982. 86

[207] S. Schmidt, D. A. Finan, A. K. Duun-Henriksen, J. B. Jorgensen, H. Madsen, H. Bengtsson, J. J. Holst, S. Madsbad, and K. Norgaard. Effects of everyday life events on glucose, insulin, and glucagon dynamics in continuous subcutaneous insulin infusion-treated type 1 diabetes: Collection of clinical data for glucose modeling. *Diabetes Technol Ther*, 14(3):210–7, Mar 2011. 86, 133, 144, 147

[208] D. M. Jensen, L. Korsholm, P. Ovesen, H. Beck-Nielsen, L. Moelsted-Pedersen, J. G. Westergaard, M. Moeller, and P. Damm. Peri-conceptional A1c and risk of serious adverse pregnancy outcome in 933 women with type 1 diabetes. *Diabetes Care*, 32(6):1046–8, 2009. 87

[209] S. Lurie and Y. Mamet. Red blood cell survival and kinetics during pregnancy. *Eur J Obstet Gynecol Reprod Biol*, 93(2):185–92, 2000. 87

[210] I. F. Casson. Pregnancy in women with diabetes–after the CEMACH report, what now? *Diabet Med*, 23(5):481–4, 2006. 87

[211] A. Garcia-Patterson, I. Gich, S. B. Amini, P. M. Catalano, A. de Leiva, and R. Corcoy. Insulin requirements throughout pregnancy in women with type 1 diabetes mellitus: three changes of direction. *Diabetologia*, 53(3):446–51, 2010. 87

[212] A. D. Wollitzer, H. Zisser, and L. Jovanovic. Insulin pumps and their use in pregnancy. *Diabetes Technol Ther*, 12 Suppl 1:S33–6, 2010. 87

[213] A. Mukhopadhyay, T. Farrell, R. B. Fraser, and B. Ola. Continuous subcutaneous insulin infusion vs intensive conventional insulin therapy in pregnant diabetic women: a systematic review and metaanalysis of randomized, controlled trials. *Am J Obstet Gynecol*, 197(5):447–56, 2007. 87

[214] D. Farrar, D. J. Tuffnell, and J. West. Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes. *Cochrane Database Syst Rev*, (3):CD005542, 2007. 87

[215] H. R. Murphy, G. Rayman, K. Lewis, S. Kelly, B. Johal, K. Duffield, D. Fowler, P. J. Campbell, and R. C. Temple. Effectiveness of continuous glucose monitoring in pregnant women with diabetes: randomised clinical trial. *BMJ*, 337:a1680, 2008. 87, 117, 127

[216] S. Brage, U. Ekelund, N. Brage, M. A. Hennings, K. Froberg, P. W. Franks, and N. J. Wareham. Hierarchy of individual calibration levels for heart rate and accelerometry to measure physical activity. *J Appl Physiol*, 103(2):682–92, 2007. 89, 119

[217] G. R. Goldberg, A. M. Prentice, W. A. Coward, H. L. Davies, P. R. Murgatroyd, C. Wensing, A. E. Black, M. Harding, and M. Sawyer. Longitudinal assessment of energy expenditure in pregnancy by the doubly labeled water method. *Am J Clin Nutr*, 57(4):494–505, 1993. 91, 115

[218] J. M. van Raaij, C. M. Schonk, S. H. Vermaat-Miedema, M. E. Peek, and J. G. Hautvast. Energy cost of walking at a fixed pace and self-paced before, during, and after pregnancy. *Am J Clin Nutr*, 51(2):158–61, 1990. 91

[219] A. M. Prentice, C. J. Spaaij, G. R. Goldberg, S. D. Poppitt, J. M. van Raaij, M. Totton, D. Swann, and A. E. Black. Energy requirements of pregnant and

lactating women. *Eur J Clin Nutr*, 50 Suppl 1:S82–110; discussion S10–1, 1996. 91, 116

[220] G. A. Borg. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc*, 14(5):377–81, 1982. 91, 118

[221] S. Brage, N. Brage, P. W. Franks, U. Ekelund, and N. J. Wareham. Reliability and validity of the combined heart rate and movement sensor Actiheart. *Eur J Clin Nutr*, 59(4):561–70, 2005. 93, 130

[222] S. Brage, N. Brage, P. W. Franks, U. Ekelund, M. Y. Wong, L. B. Andersen, K. Froberg, and N. J. Wareham. Branched equation modeling of simultaneous accelerometry and heart rate monitoring improves estimate of directly measured physical activity energy expenditure. *J Appl Physiol*, 96(1):343–51, 2004. 94, 120

[223] H. R. Murphy, G. Rayman, K. Duffield, K. S. Lewis, S. Kelly, B. Johal, D. Fowler, and R. C. Temple. Changes in the glycemic profiles of women with type 1 and type 2 diabetes during pregnancy. *Diabetes Care*, 30(11):2785–91, 2007. 107, 117, 127, 128

[224] H. R. Murphy, D. Elleri, J. M. Allen, J. Harris, D. Simmons, G. Rayman, R. C. Temple, A. M. Umpleby, D. B. Dunger, A. Haidar, M. Nodale, M. E. Wilinska, and R. Hovorka. Pathophysiology of postprandial hyperglycaemia in women with type 1 diabetes during pregnancy. *Diabetologia*, 55(2):282–93, 2012. 108

[225] ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists. Pregestational diabetes mellitus. *Obstet Gynecol*, 105(3):675–85, 2005. 108

[226] B. Zinman, N. Ruderman, B. N. Campaigne, J. T. Devlin, and S. H. Schneider. Physical activity/exercise and diabetes mellitus. *Diabetes Care*, 26 Suppl 1:S73–7, 2003. 109, 114, 132

[227] G. E. Sonnenberg, F. W. Kemmer, and M. Berger. Exercise in type 1 (insulin-dependent) diabetic patients treated with continuous subcutaneous insulin infusion. Prevention of exercise induced hypoglycaemia. *Diabetologia*, 33(11):696–703, 1990. 109

[228] A. M. Gomez, C. M. Gomez, A. Veloza, O. Munoz, and C. P. Rubio. Impact of exercise on continuously-monitored glucose levels in type 1 diabetes patients >14 years of age on insulin pump therapy. *Diabetologia*, 53, 2010. 110

[229] E. Hellmuth, P. Damm, L. Molsted-Pedersen, and I. Bendtson. Prevalence of nocturnal hypoglycemia in first trimester of pregnancy in patients with insulin treated diabetes mellitus. *Acta Obstet Gynecol Scand*, 79(11):958–62, 2000. 110, 128

[230] C. E. Garber, B. Blissmer, M. R. Deschenes, B. A. Franklin, M. J. Lamonte, I. M. Lee, D. C. Nieman, and D. P. Swain. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc*, 43(7):1334–59, 2011. 113, 114

[231] R. E. Ratner. An update on the Diabetes Prevention Program. *Endocr Pract*, 12 Suppl 1:20–4, 2006. 113

[232] C. S. Moy, T. J. Songer, R. E. LaPorte, J. S. Dorman, A. M. Kriska, T. J. Orchard, D. J. Becker, and A. L. Drash. Insulin-dependent diabetes mellitus, physical activity, and death. *Am J Epidemiol*, 137(1):74–81, 1993. 113

[233] AS Brazeau, R Rabasa-Lhoret, I Strychar, and H Mircescu. Barriers to physical activity among patients with type 1 diabetes. *Diabetes care*, 31(11):2108, 2008. 113

[234] ACOG committee opinion. Exercise during pregnancy and the postpartum period. American College of Obstetricians and Gynecologists. *Int J Gynaecol Obstet*, 77(1):79–81, 2002. 114

[235] R. Schiel, A. Thomas, A. Kaps, and G. Bieber. An innovative telemedical support system to measure physical activity in children and adolescents with type 1 diabetes mellitus. *Exp Clin Endocrinol Diabetes*, 119(9):565–8, 2011. 114

[236] A. C. van Bon, E. Verbitskiy, G. von Basum, J. B. Hoekstra, and J. H. Devries. Exercise in closed-loop control: a major hurdle. *J Diabetes Sci Technol*, 5(6):1337–41, 2011. 114, 162

[237] A. D. Stein, J. M. Rivera, and J. M. Pivarnik. Measuring energy expenditure in habitually active and sedentary pregnant women. *Med Sci Sports Exerc*, 35(8):1441–6, 2003. 114, 115, 130

[238] C. L. Harrison, R. G. Thompson, H. J. Teede, and C. B. Lombard. Measuring physical activity during pregnancy. *Int J Behav Nutr Phys Act*, 8:19, 2011. 114, 130

[239] A. M. Prentice. Stable isotopic methods for measuring energy expenditure. Applications of the doubly-labelled-water (2H2(18)O) method in free-living adults. *Proc Nutr Soc*, 47(3):259–68, 1988. 114

[240] G. Plasqui and K. R. Westerterp. Physical activity assessment with accelerometers: an evaluation against doubly labeled water. *Obesity (Silver Spring)*, 15(10):2371–9, 2007. 115

[241] V. T. van Hees, F. Renstrom, A. Wright, A. Gradmark, M. Catt, K. Y. Chen, M. Lof, L. Bluck, J. Pomeroy, N. J. Wareham, U. Ekelund, S. Brage, and P. W. Franks. Estimation of daily energy expenditure in pregnant and non-pregnant women using a wrist-worn tri-axial accelerometer. *PLoS One*, 6(7):e22922, 2011. 115

[242] E. K. Rousham, P. E. Clarke, and H. Gross. Significant changes in physical activity among pregnant women in the UK as assessed by accelerometry and self-reported activity. *Eur J Clin Nutr*, 60(3):393–400, 2006. 115, 116, 127, 130

[243] S. E. Crouter, J. R. Churilla, and Jr. Bassett, D. R. Accuracy of the Actiheart for the assessment of energy expenditure in adults. *Eur J Clin Nutr*, 62(6):704–11, 2008. 115

[244] K. Melzer, Y. Schutz, M. Boulvain, and B. Kayser. Pregnancy-related changes in activity energy expenditure and resting metabolic rate in Switzerland. *Eur J Clin Nutr*, 63(10):1185–91, 2009. 115, 116, 127, 130

[245] A. Gradmark, J. Pomeroy, F. Renstrom, S. Steiginga, M. Persson, A. Wright, L. Bluck, M. Domellof, S. E. Kahn, I. Mogren, and P. W. Franks. Physical activity, sedentary behaviors, and estimated insulin sensitivity and secretion in pregnant and non-pregnant women. *BMC Pregnancy Childbirth*, 11:44, 2011. 115, 116, 127, 130

[246] K. Melzer, Y. Schutz, M. Boulvain, and B. Kayser. Physical activity and pregnancy: cardiovascular adaptations, recommendations and pregnancy outcomes. *Sports Med*, 40(6):493–507, 2010. 115

[247] L. A. Wolfe, A. P. Heenan, and A. Bonen. Aerobic conditioning effects on substrate responses during graded cycling in pregnancy. *Can J Physiol Pharmacol*, 81(7):696–703, 2003. 115

[248] J. F. Clapp. Long-term outcome after exercising throughout pregnancy: fitness and cardiovascular risk. *Am J Obstet Gynecol*, 199(5):489 e1–6, 2008. 115

[249] M. C. de Barros, M. A. Lopes, R. P. Francisco, A. D. Sapienza, and M. Zugaib. Resistance exercise and glycemic control in women with gestational diabetes mellitus. *Am J Obstet Gynecol*, 203(6):556 e1–6, 2010. 115

[250] M. J. Ong, K. J. Guelfi, T. Hunter, K. E. Wallman, P. A. Fournier, and J. P. Newnham. Supervised home-based exercise may attenuate the decline of glucose tolerance in obese pregnant women. *Diabetes Metab*, 35(5):418–21, 2009. 115

[251] D. R. Hollingsworth and T. R. Moore. Postprandial walking exercise in pregnant insulin-dependent (type I) diabetic women: reduction of plasma lipid levels but absence of a significant effect on glycemic control. *Am J Obstet Gynecol*, 157(6):1359–63, 1987. 115, 129

[252] C. McParlin, S. C. Robson, P. W. Tennant, H. Besson, J. Rankin, A. J. Adamson, M. S. Pearce, and R. Bell. Objectively measured physical activity during pregnancy: a study in obese and overweight women. *BMC Pregnancy Childbirth*, 10:76, 2010. 116, 127

[253] M. Lof. Physical activity pattern and activity energy expenditure in healthy pregnant and non-pregnant Swedish women. *Eur J Clin Nutr*, 65(12):1295–301, 2011. 116, 127

[254] Y. Yogev, A. Ben-Haroush, R. Chen, B. Rosenn, M. Hod, and O. Langer. Diurnal glycemic profile in obese and normal weight nondiabetic pregnant women. *Am J Obstet Gynecol*, 191(3):949–53, 2004. 116

[255] L. Chitayat, H. Zisser, and L. Jovanovic. Continuous glucose monitoring during pregnancy. *Diabetes Technol Ther*, 11 Suppl 1:S105–11, 2009. 117, 135

[256] O. Cohen, N. Keidar, M. Simchen, B. Weisz, M. Dolitsky, and E. Sivan. Macrosomia in well controlled CSII treated type I diabetic pregnancy. *Gynecol Endocrinol*, 24(11):611–3, 2008. 117

[257] G. Mello, E. Parretti, F. Mecacci, P. La Torre, R. Cioni, D. Cianciulli, and G. Scarselli. What degree of maternal metabolic control in women with type 1 diabetes is associated with normal body size and proportions in full-term infants? *Diabetes Care*, 23(10):1494–8, 2000. 117

[258] A. Kerssen, H. W. de Valk, and G. H. Visser. Day-to-day glucose variability during pregnancy in women with type 1 diabetes mellitus: glucose profiles measured with the continuous glucose monitoring system. *BJOG*, 111(9):919–24, 2004. 117, 127

[259] Y. Yogev, R. Chen, A. Ben-Haroush, M. Phillip, L. Jovanovic, and M. Hod. Continuous glucose monitoring for the evaluation of gravid women with type 1 diabetes mellitus. *Obstet Gynecol*, 101(4):633–8, 2003. 117, 127

[260] G. Petrovski, C. Dimitrovski, M. Bogoev, T. Milenkovic, I. Ahmeti, and I. Bitovska. Is there a difference in pregnancy and glycemic outcome in patients with type 1 diabetes on insulin pump with constant or intermittent glucose monitoring? A pilot study. *Diabetes Technol Ther*, 13(11):1109–13, 2011. 117

[261] B. E. Ainsworth, W. L. Haskell, A. S. Leon, Jr. Jacobs, D. R., H. J. Montoye, J. F. Sallis, and Jr. Paffenbarger, R. S. Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc*, 25(1):71–80, 1993. 118, 121, 127

[262] M. Lof and E. Forsum. Activity pattern and energy expenditure due to physical activity before and during pregnancy in healthy Swedish women. *Br J Nutr*, 95(2):296–302, 2006. L. 127

[263] C. M. Peterson and L. Jovanovic-Peterson. Percentage of carbohydrate and glycemic response to breakfast, lunch, and dinner in women with gestational diabetes. *Diabetes*, 40 Suppl 2:172–4, 1991. 129

[264] G. N. Healy, D. W. Dunstan, J. Salmon, E. Cerin, J. E. Shaw, P. Z. Zimmet, and N. Owen. Objectively measured light-intensity physical activity is indepen-

dently associated with 2-h plasma glucose. *Diabetes Care*, 30(6):1384–9, 2007. 129

[265] M. Devadoss, L. Kennedy, and N. Herbold. Endurance athletes and type 1 diabetes. *Diabetes Educ*, 37(2):193–207, 2011. 132

[266] H. J. Yoo, H. G. An, S. Y. Park, O. H. Ryu, H. Y. Kim, J. A. Seo, E. G. Hong, D. H. Shin, Y. H. Kim, S. G. Kim, K. M. Choi, I. B. Park, J. M. Yu, and S. H. Baik. Use of a real time continuous glucose monitoring system as a motivational device for poorly controlled type 2 diabetes. *Diabetes Res Clin Pract*, 82(1):73–9, 2008. 133

[267] P Adolfsson, H Örnhagen, and J Jendle. The benefits of continuous glucose monitoring and a glucose monitoring schedule in individuals with type 1 diabetes during recreational diving. *J Diabetes Sci Technol*, 2(5):778–84, 2008. 133

[268] J Broz, M Brabec, and J Polak. The accuracy of real-time CGM sensor in patients with type 1 diabetes during a physical activity. In *Advanced Technologies & Treatments of Diabetes London UK*, 2011. 133, 144

[269] P. Adolfsson, S. Nilsson, and B. Lindblad. Continuous glucose monitoring system during physical exercise in adolescents with type 1 diabetes. *Acta Paediatr*, 100(12):1603–9, 2011. 133, 134, 144, 148

[270] D. M. Wilson, R. W. Beck, W. V. Tamborlane, M. J. Dontchev, C. Kollman, P. Chase, L. A. Fox, K. J. Ruedy, E. Tsalikian, S. A. Weinzimer, and Grp DirecNet Study. The accuracy of the FreeStyle Navigator continuous glucose monitoring system in children with type 1 diabetes. *Diabetes Care*, 30(1):59–64, 2007. 133, 144, 147

[271] RJ Davey, LD Ferreira, TW Jones, and PA Fournier. Effect of exercise-mediated acidosis on determination of glycemia using CGMS. *Diabetes Technol Ther*, 8(4):516–8, 2006. 134, 148

[272] K. E. Iscoe, J. E. Campbell, V. Jamnik, B. A. Perkins, and M. C. Riddell. Efficacy of continuous real-time blood glucose monitoring during and after prolonged high-intensity cycling exercise: spinning with a continuous glucose monitoring system. *Diabetes Technol Ther*, 8(6):627–35, 2006. 134

[273] T. Nunnold, S. R. Colberg, M. T. Herriott, and C. T. Somma. Use of the non-invasive GlucoWatch Biographer during exercise of varying intensity. *Diabetes Technol Ther*, 6(4):454–62, 2004. 134, 148

[274] C. Fayolle, J. F. Brun, J. Bringer, J. Mercier, and E. Renard. Accuracy of continuous subcutaneous glucose monitoring with the GlucoDay in type 1 diabetic patients treated by subcutaneous insulin infusion during exercise of low versus high intensity. *Diabetes Metab*, 32(4):313–20, 2006. 135, 148

[275] A. Kerssen, H. W. de Valk, and G. H. Visser. The continuous glucose monitoring system during pregnancy of women with type 1 diabetes mellitus: accuracy assessment. *Diabetes Technol Ther*, 6(5):645–51, 2004. 135, 144

[276] J. M. Bland and D. G. Altman. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*, 1(8476):307–10, 1986. 138

[277] C. Tack, H. Pohlmeier, T. Behnke, V. Schmid, M. Grenningloh, T. Forst, and A. Pfutzner. Accuracy evaluation of five blood glucose monitoring systems obtained from the pharmacy: A European multicenter study with 453 subjects. *Diabetes Technol Ther*, 14(4):330–7, 2011. 147

[278] K. Nerhus, P. Rustad, and S. Sandberg. Effect of ambient temperature on analytical performance of self-monitoring blood glucose systems. *Diabetes Technol Ther*, 13(9):883–92, 2011. 148

[279] F. Ricci, F. Caprio, A. Poscia, F. Valgimigli, D. Messeri, E. Lepori, G. Dall'Oglio, G. Palleschi, and D. Moscone. Toward continuous glucose monitoring with planar modified biosensors and microdialysis. Study of temperature, oxygen dependence and in vivo experiment. *Biosens Bioelectron*, 22(9-10):2032–9, 2007. 148

[280] J. R. Castle, A. Pitts, K. Hanavan, R. Muhly, J. El Youssef, C. Hughes-Karvetski, B. Kovatchev, and W. K. Ward. The accuracy benefit of multiple amperometric glucose sensors in people with type 1 diabetes. *Diabetes Care*, 35(4):706–10, 2012. 153

[281] D. Elleri, C. L. Acerini, J. M. Allen, A. M. Larsen, M. E. Wilinska, D. B. Dunger, and R. Hovorka. Effect of delay on measurement of blood glucose levels in

young subjects with type 1 diabetes. *Diabetes Res Clin Pract*, 86(2):e31–3, 2009. 155

[282] Allen J Harris J Kumareswaran K Nodale M Acerini C Wilinska M Jackson N Umpleby M Evans ML Dunger D Hovorka R Haidar A, Elleri D. Validity of triple and dual-tracer techniques to estimate glucose appearance. *Am J Physiol Endocrinol Metab.*, Mar 27 2012. 158

[283] G. E. Umpierrez, S. D. Isaacs, N. Bazargan, X. D. You, L. M. Thaler, and A. E. Kitabchi. Hyperglycemia: An independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab*, 87(3):978–82, 2002. 158

[284] L. Heinemann, C. Benesch, and J. H. DeVries. APhome: a novel European approach to bring the artificial pancreas home. *J Diabetes Sci Technol*, 5(6):1363–72, 2011. 160

[285] S. Lindpointner, S. Korsatko, G. Kohler, H. Kohler, R. Schaller, L. Schaupp, M. Ellmerer, T. R. Pieber, and W. Regittnig. Glucose levels at the site of subcutaneous insulin administration and their relationship to plasma levels. *Diabetes Care*, 33(4):833–8, 2010. 160

[286] J. C. Pickup, S. C. Freeman, and A. J. Sutton. Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. *BMJ*, 343:d3805, 2011. 161

[287] A. C. van Bon, M. J. Kohinor, J. B. Hoekstra, G. von Basum, and J. H. deVries. Patients' perception and future acceptance of an artificial pancreas. *J Diabetes Sci Technol*, 4(3):596–602, 2010. 161

[288] D. Elleri, C. L. Acerini, J. M. Allen, J. Hayes, C. Pesterfield, M. E. Wilinska, D. B. Dunger, and R. Hovorka. Parental attitudes towards overnight closed-loop glucose control in children with type 1 diabetes. *Diabetes Technol Ther*, 12(1):35–9, 2010. 161

[289] G. Lanzola, D. Capozzi, N. Serina, L. Magni, and R. Bellazzi. Bringing the artificial pancreas home: telemedicine aspects. *J Diabetes Sci Technol*, 5(6):1381–6, 2011. 163

[290] E. Dassau, L. Jovanovic, 3rd Doyle, F. J., and H. C. Zisser. Enhanced 911/global position system wizard: a telemedicine application for the prevention of severe hypoglycemia – monitor, alert, and locate. *J Diabetes Sci Technol*, 3(6):1501–6, 2009. 163