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# INSULIN PUMP THERAPY FOR TYPE 1 AND TYPE 2 DIABETES


HEALTH TECHNOLOGY ASSESSMENT SECTION
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MINISTRY OF HEALTH MALAYSIA



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**DISCLAIMER**

Technology review is a brief report, prepared on an urgent basis, which draws on restricted reviews from analysis of pertinent literature, on expert opinion and / or regulatory status where appropriate. It has been subjected to an external review process. While effort has been made to do so, this document may not fully reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion of this review.

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**DISCLOSURE**

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## EXECUTIVE SUMMARY

### Background

People with diabetes mellitus are generally divided into two types of diabetes namely type 1 and type 2 diabetes. Type 1 diabetes involves a process of destruction of the β-cells of pancreas, leading to severe insulin deficiency, so that insulin treatment is required for survival. Type 2 diabetes is linked to overweight and obesity and to physical inactivity. Poor control of diabetes, reflected in high blood glucose levels, can in situations of severe stress in people with type 2 diabetes or withdrawal of insulin in those with type 1 diabetes, result in diabetic ketoacidosis, a serious and potentially fatal condition, and in the long term increase the risk of complications such as diabetic retinopathy, neuropathy and nephropathy. However, good diabetic control reduces the risk of the above-mentioned complications. Type 2 diabetes is also known to be progressive – with gradual but inexorable loss of β-cells function over time, such that many will eventually require insulin for glycaemic control.

Insulin therapy remains an effective therapeutic modality to control blood glucose. In normal non-diabetic condition, our body requires a little insulin throughout the day (ie basal insulin). The consumption of food stimulates the release of insulin by the pancreas. The challenge in currently available insulin for patients with diabetes is the difficulty in matching insulin with the physiological requirements of basal insulin as well as in response to ingestion of food. Therefore, continuous subcutaneous insulin infusion (CSII) using insulin pump is a new therapeutic strategy that answers some of the challenges in patients on multiple daily injections (MDI) for control of glucose.

The concept of insulin pump therapy was first introduced by Arnold Kadish in Beverly Hills, CA, in the 1960s. However, it was not until the early 1980s that the first FDA-approved pump became available for use by people with type 1 diabetes. Insulin pump therapy has been used in developed countries like United Kingdom, United States and Australia as mainstream treatment for diabetes patients especially patients with type 1 diabetes.

The basic concept of insulin pump is to use a small electronic device that is worn externally to deliver precise doses of rapid-acting insulin to closely match patients' insulin needs.

Basal rate of small amounts of insulin are delivered continuously (24/7) for normal functions of the body (not including food consumption). The programmed rate is normally determined by utilising information from the patients' usual total daily insulin requirements.

During food consumption, insulin pump is programmed to deliver a calculated insulin dose according to the carbohydrate ingested. The insulin pump has a bolus calculator built in to help patients calculate the bolus dose of insulin based on pre-determined settings. The programming of these settings should be made by trained healthcare professionals, well-versed in the management of this specialised treatment modality.

The safety and effectiveness of insulin pumps are measured by parameters such as glycated haemoglobin level ($HbA1_C$), insulin dose needed, proportion of time spent in hyperglycaemia and hypoglycaemia range, weight change, patient preference, as well as quality of life.

This review was requested by Dr. Zanariah Hussein, Head of Endocrinology Services, Ministry of Health as insulin pump therapy is not widely used in Malaysia despite having many patients, particularly young type 1 diabetes. It is also requested to assist in assessing the suitability for reimbursement in those who cannot afford this therapy.

**Objective/aim**

To assess the effectiveness, safety and cost-effectiveness of insulin pump therapy compared with multiple daily injections for type 1 and type 2 diabetes.

**Results and conclusions**

The search yielded 497 articles. After the initial screening, 11 articles consisting of three health technology assessment reports, two Cochrane systematic reviews reports, one systematic review report, three randomised-controlled trials and two cohort studies were appraised and included in this report.

**Safety**

**Type 1 Diabetes**

There was no significant difference between the hypoglycaemic events for CSII and MDI in most trials.

There was no significant difference between CSII and MDI, although the absolute number of ketoacidosis episodes was higher with CSII. The number of ketoacidosis episodes could be reduced with the usage of newer generation CSII and the proper management and training for the usage of CSII.

**Type 2 Diabetes**

In type 2 diabetes patients, only limited hyperglycaemia, hypoglycaemia and ketoacidosis cases were reported in the studies.

**Pregnancy**
There was no significant difference in maternal hypoglycaemia and hyperglycaemia events between CSII and MDI.

**Effectiveness**

**Type 1 Diabetes**
**Glycated haemoglobin level (HbA1c) reduction**
Greater reduction of glycated haemoglobin in the CSII compared to MDI. However, the difference did not reach statistical significance in some studies.

Some studies reported significant reduction of glycated haemoglobin in patients treated with CSII compared with MDI during short term follow-up (up to four months) and in those with inadequate glycaemic control.

**Insulin dosage**
Studies showed reduction in insulin dosage with CSII as compared to MDI.

**Quality of life (QoL)**
HTA reports reported no significant difference in Quality of life (QoL) for CSII compared with MDI. However, for adult patients with inadequate glycemic control, significant improvement in various aspects of QoL was observed in CSII groups compared with the MDI groups.

**Type 2 Diabetes**
**Glycated haemoglobin level (HbA1c) reduction**
There were limited studies that showed the effectiveness of CSII (reduction of HbA1c) as compared with MDI.

**Insulin dosage**
No retrievable evidence on the insulin dosage reduction with CSII as compared to MDI.

**Quality of life (QoL)**
No retrievable evidence on quality of life.

**Pregnancy**
**Glycated haemoglobin level (HbA1c) reduction**
There was lower glycated haemoglobin in CSII than MDI but the differences were not statistically significant.

No significant difference in pregnancy outcome such as macrosomia and operative birth.

**Insulin dosage**
Lower insulin units were needed for the CSII as compared to MDI.

**Quality of life (QoL)**

No retrievable evidence on the quality of life.

**Cost/Cost-Effectiveness**

One HTA report stated the estimated additional cost of CSII compared to MDI varies from £1091 per annum to £1680 per annum, according to the type of the insulin pump and the estimated life of the device. These estimates include the costs for the insulin pump, the consumables associated with delivery of CSII, and an allowance for the initial education required when patients switch from MDI to CSII.

A cost utility analysis compared the CSII and MDI reported the incremental cost-effectiveness ratio (ICER) with CSII was £11,461. (standard deviation: £3,656).

**Methods**

Electronic databases were searched through the Ovid interface: Ovid MEDLINE® In-process and other Non-indexed citations and Ovid MEDLINE® 1948 to present, EBM Reviews – Cochrane Central Register of Controlled Trials – February 2015, EBM Reviews – Cochrane Database of Systematic Reviews – 2009 to February 2015, EBM Reviews – Health Technology Assessment – 1st Quarter 2015, EBM Reviews – Database of Abstracts of Reviews of Effects – 1st Quarter 2015, EBM Reviews – NHS Economic Evaluation Database 1st Quarter 2015, Embase – 1988 to 2015 week 9. Searched were also run in PubMed. Google was used to search for additional web-based materials and information.

A critical appraisal of the retrieved papers was performed and the evidence level was graded according to the US/Canadian Preventive Services Task Force.

# INSULIN PUMP THERAPY FOR TYPE 1 AND TYPE 2 DIABETES

## 1. BACKGROUND

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Insulin therapy remains an effective therapeutic modality to control blood glucose. In normal non-diabetic condition, our body requires a little insulin throughout the day (ie basal insulin). The consumption of food stimulates the release of insulin by the pancreas. The challenge in currently available insulin for patients with diabetes is the difficulty in matching insulin with the physiological requirements of basal insulin as well as in response to ingestion of food. Therefore, continuous subcutaneous insulin infusion (CSII) using insulin pump is a new therapeutic strategy that answers some of the challenges in patients on multiple daily injections (MDI) for control of glucose.

The concept of insulin pump therapy was first introduced by Arnold Kadish in Beverly Hills, CA, in the 1960s. However, it was not until the early 1980s that the first FDA-approved pump became available for use by people with type 1 diabetes.[1] Insulin pump therapy has been used in developed countries like United Kingdom, United States and Australia as mainstream treatment for diabetes patients especially patients with type 1 diabetes.

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Basal rate of small amounts of insulin are delivered continuously (24/7) for normal functions of the body (not including food consumption). The programmed rate is normally determined by utilising information from the patients' usual total daily insulin requirements.[2]

During food consumption, insulin pump is programmed to deliver a calculated insulin dose according to the carbohydrate ingested. The insulin pump has a bolus calculator built in to help patients calculate the bolus dose of insulin based on pre-determined settings. The programming of these settings should be made by trained

healthcare professionals, well-versed in the management of this specialised treatment modality.

The safety and effectiveness of insulin pumps are measured by parameters such as glycated haemoglobin level ($HbA1_C$), insulin dose needed, proportion of time spent in hyperglycaemia and hypoglycaemia range, weight change, patient preference, as well as quality of life.

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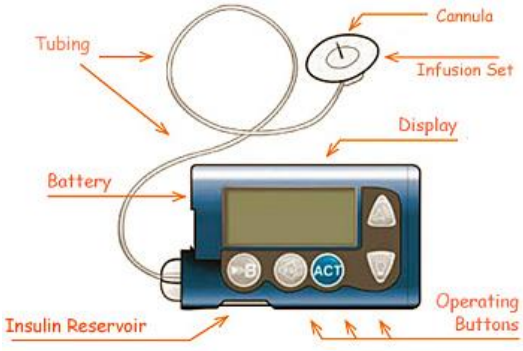
## 2. OBJECTIVE/AIM

To assess the effectiveness, safety and cost-effectiveness of insulin pump therapy compared with multiple daily injections for type 1 and type 2 diabetes.

## 3. TECHNICAL FEATURES[2]


MiniMed ® 530G with Enlite ® Sensor (multiple colour selection)[2]




MiniMed ® 530G with Enlite ® Sensor operation chart


CareLink Personal Therapy Management Software

Simple Insulin pump therapy, or continuous subcutaneous insulin infusion (CSII) set consists of four main components, namely insulin pump, reservoir, infusion set and infusion set insertion device (only in some models). Insulin pump is a small medical device that is use to program insulin, having a LCD screen to show what is programmed, a battery compartment to hold 1 AAA alkaline battery and a reservoir compartment that holds insulin.

A reservoir is a plastic cartridge that holds the insulin that is locked into the insulin pump. It comes with a transfer guard (blue piece at the top) that assists with pulling the insulin from a vial into the reservoir. A reservoir can hold up to 300 units of insulin and is changed every two to three days.

An infusion set includes a thin tube that goes from the reservoir to the infusion site on the patients' body. The cannula is inserted with a small needle that is removed after it is in place. It goes into sites (areas) on patients' body similar to where the given insulin is injected. The infusion set is changed every two to three days.

An infusion set is placed into the insertion device and with a push of a button the infusion set is inserted to the subcutaneous area of the patients.[2] Besides, infusion set with straight needle for direct insertion without using an insertion device is also available.

With the improvement of technology, a continuous subcutaneous glucose monitoring (CGM) device is introduced to enable easy monitoring of blood glucose level. CGM is a device attached to the subcutaneous area and it has a sensor link that communicates glucose readings to the pump using a radio transmitter to detect the reading of blood sugar level. Therefore, the glucose level can be traced and recorded.

This insulin delivery system that combines an external insulin pump with continuous monitoring of glucose levels via a subcutaneous sensor is called open-loop insulin delivery system.

An effective alternative to open-loop insulin delivery is closed-loop delivery, in which the involvement of the patient in maintaining glucose control is minimal. Basically the closed-loop delivery system involves the programming of an algorithm in the insulin pump to calculate the basal and bolus rate of insulin through the insulin pump. This closed-loop technology is still undergoing research to ensure safety of the algorithms utilised. However, one of the key improvements in the closed-loop system is the ability to sense low glucose and programming the CSII pump to temporarily suspend insulin, especially at night, when patients are considered to be at high risk of.[3]

## 4. METHODS

### 4.1. Searching

Electronic databases searched through the Ovid interface (examples);

- MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to present
- EBM Reviews - Cochrane Central Register of Controlled Trials-1st Quarter 2015
- EBM Reviews – Database of Abstracts of Review of Effects (1st Quarter 2015)
- EBM Reviews - Cochrane database of systematic reviews - 2005 to February 2015
- EBM Reviews - Health Technology Assessment – 1st Quarter 2015
- NHS economic evaluation database – 1st Quarter 2015

Other databases (example);

- PubMed
- Horizon Scanning database (National Horizon Scanning Centre, Australia and New Zealand Horizon Scanning Network, National Horizon Scanning Birmingham)
- FDA website
- INAHTA
- MHRA

Google was used to search for additional web-based materials and information

Additional articles such as from reviewing the bibliographies of retrieved articles or contacting the authors

Appendix 1 showed the detailed search strategies.

## 4.2. Selection

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full-text articles for final article selection.

The inclusion and exclusion criteria were:

Inclusion criteria

| | |
|---|---|
| Population | Type 1 diabetes or Type 2 diabetes patients |
| Interventions | Insulin pump therapy |
| Comparators | Conventional insulin injection<br>Multiple Doses Insulin Injection |
| Outcomes | • safety<br>- diabetes ketoacidosis<br>- adverse events<br>- hypoglycaemia<br>- Hyperglycaemia<br>• efficacy/effectiveness<br>- mean glycated haemoglobin (HbA1c)<br>- insulin dosage<br>- quality of life<br>• economic evaluation<br>- cost<br>- cost analysis<br>- cost-effectiveness |
| Study design | Health Technology Assessment (HTA), Systematic Review, Randomised control trial (RCT), cohort studies |
| | English full text articles |

Exclusion criteria

| | |
|---|---|
| Study design | Case series, case reports, surveys, anecdotal |
| | Non English full text articles |

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) and evidence graded according to the US / Canadian Preventive Services Task Force (Appendix 2).

## 5. RESULTS AND DISCUSSION

Three health technology assessment report, two Cochrane systematic reviews, one systematic review, three recent randomized controlled trials, two cohort studies including a local study were included in this therapeutic review report.

### 5.1 SAFETY

The safety of insulin pump is usually measured with the events of hypoglycaemia and hyperglycaemia. Besides, events of diabetic ketoacidosis (DKA) were also considered in the safety of the comparison between insulin pump and multiple dose insulin injections.

#### 5.1.1 Type 1 Diabetes

**Adverse effects**

**Hypoglycaemic events**

Colquitt JL et al. in the health technology assessment (HTA) report concluded that hypoglycaemic events did not differ significantly between CSII and MDI in most trials, but two found fewer hypoglycaemic episodes with CSII (Bode 1996, Brinchmann-Hansen 1988), and one study found more hypoglycaemia and hypoglycaemic coma with CSII (Zieglar 1990). [4 level I]

Cote B et al. in the health technology assessment report stated that randomized, controlled trials have found no difference, in children or adults, in the incidence of severe hypoglycaemic episodes with CSII compared to MDI. [5 level I]

Campbell S et al. in the systematic review report stated that: [6 level I]

- In adults with type 1 diabetes, two studies (DeVries 2002 and Hoogma 2006) showed infrequent of severe hypoglycaemia episodes but were consistently lower during treatment with CSII compared with MDI.

- In children and/or adolescents with type 1 diabetes, three trials (Cohen 2003, Doyle 2004 and Weintrob 2003) reported episodes of severe hypoglycaemia were less frequent during treatment with CSII compared with MDI.

Bolli GB et al. in a randomised controlled study comparing CSII and MDI reported the incidence of hypoglycaemia was similar with CSII and MDI for overall (41 ± 43 vs. 35 ± 35 events/patient; P=0.93) [7 level I].

Bergenstal RM et al. in a 1-year, multicenter, randomized, controlled trial stated that the rate of severe hypoglycaemia in the CSII group (13.31 cases per 100

person-years) did not differ significantly from that in the MDI group (13.48 per 100 person-years, P=0.58). [8 level I]

**Diabetic Ketoacidosis (DKA)**

Colquitt JL et al. in the HTA report stated that two studies reported no occurrences of ketoacidosis while another three studies reported no events with MDI and one or two episodes with CSII. Greater numbers of such episodes were reported in older studies.[4 level I]

Cote B et al. stated that as for the incidence of ketoacidosis episodes, studies have found no significant difference between CSII and MDI, although the absolute number of ketoacidosis episodes was higher with the CSII.[5 level I]

Campbell S et al. in the systematic review report stated that: [6 level I]

- In adults with type 1 diabetes, ketoacidosis events were uncommon but occurred more frequently during treatment with CSII compared with MDI.

- In children and/or adolescents with type 1 diabetes, ketoacidosis events were uncommon with both treatment modalities and therefore no firm conclusions can be drawn.

### 5.1.2 Type 2 Diabetes

Campbell S et al. in the systematic review report stated that: [6 level I]

- In adults with type 2 diabetes, the total number of severe hypoglycaemic across four trials was higher in patients treated with MDI; however, this was driven by only one trial (Herman 2005). Two of the trials (Berthe 2007 and Raskin 2003) reported no cases of severe hypoglycaemia and one trial (Wainstein 2005) reported more episodes in during treatment with CSII.

Reznik Y et al. conducted a multicentre, controlled trial at 36 hospitals, tertiary care centres, and referral centres in Canada, Europe, Israel, South Africa, and USA that included patients with type 2 diabetes who had poor glycaemic control despite MDI with insulin analogues. [9 level I] For the safety of the CSII, the study reported that:

- Five episodes of hyperglycaemia related to device or study procedure in the pump treatment group, which did not result in hospital admission.

- Three diabetes-related serious adverse events (hyperglycaemia or ketoanemia without acidosis) resulting in admission to hospital occurred (two in the CSII group, one in the MDI group). No episodes of ketoacidosis occurred in either group during the study. One episode of severe

hypoglycaemia occurred in the MDI groups, in a female developed confusion and had a blood glucose concentration of 1.7mmol/L.

### 5.1.3 Pregnancy

Farrar D, Tuffnell DJ, West J in a Cochrane review on CSII versus MDI for pregnant women with diabetes reviewed that: [7 level I]

- There were no significant differences in maternal hypoglycaemia (RR 3.00, 95% CI 0.35 to 25.87) in two trials and 61 pregnancies.

- There were no significant differences in maternal hyperglycaemia (RR 7.00, 95% CI 0.39 to 125.44) in two trials and 61 pregnancies.

## 5.2. EFFICACY/ EFFECTIVENESS

The aim of this report was to assess the effectiveness of insulin pump as compared to conventional multiple doses insulin injection. Therefore, the outcomes that used to measure the effectiveness between these two technologies includes the measurement of outcome of glycaemic control including glycated haemoglobin $HbA_{1c}$, mean blood glucose, insulin dose and the outcome of quality of life.

### 5.2.1 Type 1 Diabetes

**Adult**

**Glycated haemoglobin $HbA1_c$**

Colquitt JL et al. in the HTA report which included 14 studies for adults with type 1 diabetes (baseline glycated hemoglobin ranged from 7.7% to 13.2%) stated that:[4 level I]

- Four randomised trials reported glycated haemoglobin at ten weeks to four months of follow-up with the pooling of data using random-effects model ($X^2$ test for heterogeneity 12.95, df=3, p=0.0047) showed a significant reduction in glycated haemoglobin with CSII compared with MDI (weighted mean difference (WMD) -0.87%, 95% Confidence Interval (CI)-1.59 to -0.16).

- Two randomised trials reported glycated haemoglobin at six months of follow-up with the pooling of data using random-effects model ($X^2$ test for heterogeneity 1.08, df=1, p=0.3) showed a non-significant reduction in glycated haemoglobin with CSII compared with MDI (WMD -0.28%, 95% CI -0.64 to 0.08).

Cote et al. in the HTA report stated that: [5 level I]

- For patients selected because of inadequate glycemic control (HbA1c level ≥ 8.5%), DeVries et al. in the randomised controlled trial noted a significant decreased in the glycated haemoglobin level with CSII

compared with MDI after four months of follow-up (-0.84, 95% CI: -1.31 to -0.36; p=0.002).

Campbell S et al. in the systematic review stated that: [6 level I]

- For type 1 diabetes patients, two RCTs (DeVries 2002, Hoogma 2006) that compared CSII with MDI found that the CSII was associated with a greater reduction in glycated haemoglobin levels compared to the MDI. However, meta-analysis on the studies favoured insulin pump but show no significant difference between CSII and MDI in terms of glycated haemoglobin reduction at 3-4 months (WMD -0.45%, 95% CI, -1.04 to 0.14). This is likely due to significant heterogeneity between the trials.

Misso ML et al. conducted a Cochrane systematic review on the effectiveness of CSII compared to MDI for type 1 diabetes patients stated: [11 level I]

- There was a statistically significant difference in glycated haemoglobin favouring CSII (WMD -0.3% (95% CI, -0.1 to -0.4, P=0.01).

Bolli GB et al. conducted a randomised controlled trial in type 1 diabetic patients comparing CSII with MDI.[7 level I] Twenty four participants were included in CSII group while 26 participants in MDI group. The report stated that:

- Mean glycated haemoglobin fell similarly in the two groups (CSII -0.7±0.7%; MDI -0.6±0.8%) with a baseline-adjusted difference of -0.1% (95%CI, -0.5 to 0.3).

**Insulin Dosage**

Colquitt et al. pooled data of four studies into a meta-analysis using a random-effects model ($X^2$ test for heterogeneity 3.78, df=3, p=0.29) showed that:[4 level I]

- Overall significant reduction in insulin dose with CSII of about 12 units per day (-11.90, 95% CI, -18.16 to -5.63) for a ten weeks to four months treatment.

Bolli GB et al. showed that: [7 level I]

- The total insulin requirement at end point was 36.2±11.5 units/day on CSII and 42.6±15.5 units/day on MDI indicating that less insulin was required for CSII.

**Quality of life (QoL)**

Colquitt JL et al. in the HTA reported: [4 level I]

- Only one study (Tsui 2001) reported on QoL. Information was collected using the Diabetes Quality of Life (DQoL) tool. No significant differences between CSII and MDI were found overall or on any of the subscales: satisfaction (7.3), impact (1.5), diabetic worry (5.4), global health (0.9) or social worry (-4.4).

Cote et al. in the HTA reported:[5 level I]

- The data on the impact of the CSII on quality of life from randomised or cohort studies involving the general population of type 1 diabetics did not indicate any improvement.

- In adult patients selected because of inadequate glycaemic control, two studies reported CSII led to a significant improvement in various aspects of quality of life.

Misso ML et al. in the Cochrane Review stated that Quality of life measures mostly using validated diabetes treatment satisfaction questionnaire (DTSQ), validated diabetes quality of life for youth scale (DQOLY) and validated diabetes quality of life scale (DQoL) suggested that: [11 level I]

- CSII was preferred over MDI with most studies having higher scores for the CSII groups than MDI groups.

**Adolescents**

**Glycated haemoglobin $HbA_{1c}$**

Colquitt JL et al. stated that there were two randomised crossover studies which compared the effects of MDI and CSII in adolescents aged up to 20 years with type 1 diabetes.[4 level I]

- Schriffrin et al. included treatment with CSII alone, MDI alone and CSII overnight plus MDI during the day (CSII + MDI). After one month, glycated haemoglobin was significantly lower than baseline [13% (SD1), $p<0.001$] in all three groups. At four months of follow-up, glycated haemoglobin was significantly lower with CSII (8.8%) than with MDI (9.6%, $p<0.05$) or CSII + MDI (9.3%, $p<0.05$). They found no significant difference between CSII and MDI after six months of follow-up (8.5% versus 8.7%, p=ns).

- Tamborlene et al. found a decrease in glycated haemoglobin with both CSII and MDI compared with baseline ($p<0.05$), they found no significant difference between CSII and MDI after six months of follow-up (8.5% versus 8.7%, p=ns).

**Insulin Dosage**

Schriffrin et al. stated:

- Total daily insulin dose was significantly lower during both CSII (44U/day) and CSII + MDI (48U/day) than at baseline [64U/day (SD 14), $p<0.001$] or during MDI (60 U/day, $p<0.001$).

Tamborlene et al. stated:

- An increase in insulin dose with both CSII and MDI compared with baseline ($p<0.05$), but no significant difference between CSII and MDI after 6 months of follow-up (1.3 versus 1.4U/day, p=ns).

**Children**

Colquitt et al. stated: [4 level I]

- There was no published randomised trial found.

- Case series suggested that CSII has a place in treatment of children with diabetes, but this needs to be confirmed in randomised studies.

**Glycated haemoglobin $HbA_{1c}$**

Cummins E et al. in the HTA report stated:[12 level I]

- For children and adolescents, one trial (Doyle 2004) reported that glycated haemoglobin was significantly lower on CSII than on MDI.

Campbell S et al. in the systematic review stated:[6 level I]

- In children and adolescents with type 1 diabetes, the meta-analysis of three trials favour MDI when adjusted for baseline glycated haemoglobin levels but revealed no significant difference between treatments in terms of glycated haemoglobin at endpoint (WMD -0.31%, 95% CI, -0.79 to 0.16%). The difference between CSII and MDI in terms of change from baseline glycated haemoglobin, weighted by sample size, was 0.33% in favour of CSII.

Stephanie R. et al. conducted a cohort study on long term outcome of insulin pump therapy in children with type 1 diabetes.[13 Level II-2] The patients on pump therapy were matched to patients treated by injections on the basis of age, duration of diabetes and glycated haemoglobin at the time of pump start. The report stated:

- The mean difference of glycated haemoglobin between the pump and non-pump cohort was 0.6% over the 7 years of follow-up.

- Once on insulin pump therapy, the pump cohort had a significantly improved glycated haemoglobin at all time-points (three months, twelve months, six monthly until two years and yearly thereafter), with an initial rapid improvement in the pump versus non-pump groups of 0.6% (6.6 mmol/mol) at three months ($p<0.001$).

- The level of improvement was lowest at two years, although still significant at 0.3% (3.3 mmol/mol, $p=0.01$).

- The improvement in the pump cohort increased from year two to seven, reaching a maximum of 1.0% (10.9 mmol/mol, $p<0.01$) at six years.

Another cohort was a local retrospective cohort study by Ooi et al. to evaluate the effectiveness of insulin pump usage in Malaysia UKM hospital.[14 level II-2] Eighteen patients with mean age of 14.6±5.5 years old who were on CSII from April 2004 to December 2009 were studied. The annual mean glycated haemoglobin dropped 0.6% in the first year of pump use (8.1±1.2%) when compared with glycated haemoglobin at the start of treatment (8.7±1.5%).

**Quality of life (QoL)**

Cote et al. stated:[5 level I]

- For diabetic children, randomised, controlled trials reported no significant effect on the quality of life of children who used the pump. Only one such trial found a tendency in favour of CSII with regard to certain domains covered by the diabetes quality of life for youth scale (DQOLY) questionnaire, particularly satisfaction with the treatment.

**Insulin Dosage**

Weintrob N et al. stated that there was a significant interaction between the therapy regimen and the change in insulin dose over time, decreasing during pump therapy and increasing during MDI (P= .003). [15 level I]

**Adult and Children**

Bergenstal RM et al. in a 1-year, multicenter, randomized, controlled trial comparing sensor-augmented CSII and MDI that involved 329 adults and 156 children) with inadequately controlled type 1 diabetes concluded:[8 level I]

- Baseline mean glycated hemoglobin level (8.3% in the two study groups) had decreased to 7.5% in the CSII group, as compared with 8.1% in the MDI group, for a between-group difference in the CSII group of -0.6 percentage points (95% CI, -0.7 to -0.4; P<0.001).

### 5.2.2 Type 2 Diabetes

Colquitt JL et al. in the HTA stated:[4 level I]

- There was little evidence in the study of CSII usage for Type 2 Diabetes patients. Valensi et al. carried out a short-term study, duration eight to twenty three days, but CSII was combined with metformin, and with strict diet, in patients admitted to hospital. Little can be deduced about CSII from this study.

- Dupuy O et al. studied all their type 2 diabetes patients with poor control on maximal oral therapy. A group of 111 remained on oral treatment apart from two 3-day periods on CSII, and their glycated haemoglobin improved from 8.76% at the start of the period to 7.82% at the end. The writer concluded that there may be a place for short-term use of CSII, but further research is required.

Cummins E et al. in the HTA report stated:[12 level I]

- For type 2 diabetes patients, there was little evidence that CSII was better than MDI.
- Berthe reported that glycated haemoglobin decreased significantly more in patients at the end of the CSII period compared to end of MDI period.
- The other two studies (Wainstein 2005, Raskin 2003) reported no significant difference between groups; although both CSII and MDI

reduced glycated haemoglobin significantly between baseline and end of study ($p<0.05$).

Reznik Y et al. conducted a randomised open-label controlled trial to compare the use of CSII and MDI in patients with type 2 diabetes.[9 level I] The primary endpoint was the between-group difference in change in mean glycated haemoglobin from baseline to the end of the randomised phase. The baseline mean glycated haemoglobin was 9.0% (75mmol/mol) in both groups. Secondary endpoints included changes from baseline to six months of continuous glucose monitoring data, including mean 24-h glucose concentrations, the area under the curve (AUC) for hypoglycaemia (defined as sensor glucose values <3.9 mmol/L) and hyperglycaemia (sensor glucose values >10 mmol/L), and the time spent in hypoglycaemia and hyperglycaemia. As a conclusion:

- CSII group showed decrease in baseline mean glycated haemoglobin (mean change -1.1%, SD 1.2; -12 mmol/mol, SD 13). MDI group (-0.4%, SD 1.1; -4 mmol/mol, SD 12). The difference between the two groups was -0.7% (95% CI -0.9 to -0.4; -8 mmol/mol, 95% CI -10 to -4 mmol/mol, adjusted $p<0.0001$)

### 5.2.3 Pregnancy

**Glycated haemoglobin $HbA_{1c}$**

Colquitt et al. stated four parallel RCTs compared the effects of CSII with MDI in pregnancy. During the first trimester, glycated haemoglobin was lower with CSII than MDI (0.2 – 1.1%) in both type 1 and type 2 diabetes, but these differences were not statistically significant. Similarly, there were no significant differences between CSII and MDI during the second trimester (-0.7 to 0.75%) or term (-0.1 to 0.7%).[4 level I]

**Macrosomia and Operative birth**

Farrar D, Tuffnell DJ, West J conducted a Cochrane systematic review on the CSII versus MDI for pregnant women.[10 level I]

- Two trials with 61 pregnancies found that there was no significant difference in macrosomia (birthweight greater than 4000 g) (risk ratio (RR) 3.20, 95% CI 0.14 to 72.62).

- Three trials with 71 pregnancies found that there was no significant difference in risk of operative birth, caesarean birth (RR 1.09, 95% CI 0.66 to 1.77).

**Quality of life (QoL)**

Colquitt et al. reported that patients' preference and quality of life were not reported by the four studies comparing CSII and MDI in pregnancy.[4 level I]

**Insulin Dosage**

Colquitt et al. reported that there was no significant difference between CSII and MDI in total daily insulin dose in type 1 and type 2 diabetes pregnancy. However, Coustan et al. found that fewer insulin units per kilogram per day were required with CSII than with MDI [first trimester, 0.71U/kg/day (SD 0.16) versus 1.01 U/kg/day (SD 0.28), p=0.101; second trimester 1.02 U/kg/day (SD 0.53) versus 1.40 U/kg/day (SD 0.4). p=0.027; third trimester, 1.26 U/kg/day (SD 0.49) versus 1.63 U/kg/day (SD 0.51), p=0.041].[4 level I]

## 5.3 COST/COST-EFFECTIVENESS

Colquitt JL et al. stated:[4 level I]

- No economic evaluations comparing CSII with MDI were identified.

- The estimated additional cost of CSII compared to MDI varies from £1091 per annum to £1680 per annum, according to the type of the insulin pump and the estimated life of the device. These estimates include the costs for the insulin pump, the consumables associated with delivery of CSII, and an allowance for the initial education required when patients switch from MDI to CSII.

Cote B et al. in the report stated that:[5 level I]

- The Quebec-based cost analysis of CSII compared to MDI showed an additional cost of CA$4,746 per user.

- 8-year Markov model (Scuffham and Carr, 2003) constructed to compare the costs and utility of CSII and MDI. The model showed the incremental cost per QALY gained (ICER) with the pump was £11,461 (Standard deviation: £3,656).

## 5.4 ORGANIZATIONAL

Patients using CSII has to be trained on the CSII usage. Training on handling of the consumable items (e.g. infusion sets) is also important to prevent the complication due to the improper use of the CSII devices.

## 5.4 LIMITATIONS

Our study has several limitations. The selection of the studies and appraisal was done by one reviewer. Although there was no restriction in language during the search, only English full text articles were included in the report.

## 6. CONCLUSION

### Safety

**Type 1 Diabetes**

There was no significant difference between the hypoglycaemic events for CSII and MDI in most trials.

There was no significant difference between CSII and MDI, although the absolute number of ketoacidosis episodes was higher with CSII. The number of ketoacidosis episodes could be reduced with the usage of newer generation CSII and the proper management and training for the usage of CSII.

**Type 2 Diabetes**

In type 2 diabetes, only limited hyperglycaemia, hypoglycaemia and ketoacidosis cases were reported in the studies.

**Pregnancy**

There was no significant difference in maternal hypoglycaemia and hyperglycaemia events between CSII and MDI.

### Effectiveness

**Type 1 Diabetes**

**Glycated haemoglobin level (HbA1c) reduction**

Greater reduction of glycated haemoglobin in the CSII compared to MDI. However, the difference did not reach statistical significance in some studies.

Some studies reported significant reduction of glycated haemoglobin in patients treated with CSII compared with MDI during short term follow-up (up to four months) and in those with inadequate glycaemic control.

**Insulin dosage**

Studies showed reduction in insulin dosage with CSII compared to MDI.

**Quality of life (QoL)**

HTA reports reported no significant difference in Quality of life (QoL) for CSII compared with MDI. However, for adult patients with inadequate glycaemic control, significant improvement in various aspects of QoL was observed in CSII groups compared with the MDI groups.

**Type 2 Diabetes**

**Glycated haemoglobin level (HbA1c) reduction**

There were limited studies that showed the effectiveness of CSII (reduction of HbA1c) as compared with MDI.

**Insulin dosage**

No retrievable evidence on the insulin dosage reduction with CSII as compared to MDI.

**Quality of life (QoL)**
No retrievable evidence on the quality of life.

**Pregnancy**
**Glycated haemoglobin level (HbA1c) reduction**
There was lower glycated haemoglobin in CSII than MDI but the differences were not statistically significant.

No significant difference in pregnancy outcome such as macrosomia and operative birth.

**Insulin dosage**
Lower insulin units were needed for the CSII as compared to MDI.

**Quality of life (QoL)**
No retrievable evidence on the quality of life.

**Cost/Cost-Effectiveness**

One HTA report stated the estimated additional cost of CSII compared to MDI varies from £1091 per annum to £1680 per annum, according to the type of the insulin pump used and the estimated life of the device. These estimates include the costs for the insulin pump, the consumables associated with delivery of CSII, and an allowance for the initial education required when patients switch from MDI to CSII.

A cost utility analysis compared the CSII and MDI reported the incremental cost-effectiveness ratio (ICER) with CSII was £11,461. (standard deviation: £3,656).

## 7. REFERENCES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population-based case-control study. Diabetologia. 2013; 56(11):2392-2400.
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# 8. APPENDIX

## 8.1. Appendix 1: LITERATURE SEARCH STRATEGY

**Ovid MEDLINE® In-process & other Non-Indexed citations and OvidMEDLINE® 1948 to present**

1 Diabetes Mellitus, Type 1/ (62091)
2 (diabetes adj1 (autoimmune or juvenile-onset or juvenile onset or mellitus sudden-onset)).tw. (2977)
3 ((diabetes mellitus or diabetes mellitus 1) adj1 (type i or brittle or sudden onset or sudden-onset or insulin-dependent or ketosis-prone or juvenile-onset or insulin-dependent 1 or insulin dependent or juvenile onset or ketosis prone or type 1)).tw. (23873)
4 iddm.tw. (6718)
5 1 or 2 or 3 or 4 (73241)
6 Diabetes Mellitus, Type 2/ (88842)
7 ((diabetes mellitus or diabetes) adj1 (maturity onset or adult-onset or non-insulin-dependent or type ii or stable or ketosis-resistant or maturity-onset or type 2 or slow onset or adult onset or noninsulin dependent or slow-onset or ketosis resistant or noninsulin-dependent)).tw. (87131)
8 mody.tw. (899)
9 niddm.tw. (6814)
10 6 or 7 or 8 or 9 (120850)
11 5 or 10 (174704)
12 Insulin Infusion Systems/ (3946)
13 (system* adj1 insulin infusion).tw. (180)
14 insulin infusion system*.tw. (164)
15 ((insulin pump or insulin) adj1 (programmable implantable or implantable programmable or pump programmable implantable)).tw. (10)
16 12 or 13 or 14 or 15 (4050)
17 11 and 16 (2545)
18 limit 17 to (humans and (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial or systematic reviews)) (497)

| **OTHER DATABASES** | |
|---|---|
| EBM Reviews - Cochrane Central Register of Controlled Trials | |
| EBM Reviews - Database of Abstracts of Review of Effects | |
| EBM Reviews - Cochrane database of systematic reviews | Same MeSH, keywords, limits used as per MEDLINE search |
| EBM Reviews - Health Technology Assessment | |
| PubMed | |
| NHS economic evaluation database | |
| INAHTA | |
| FDA | |

## 8.2. Appendix 2

## DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

***SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris S2001)***

## 8.3. Appendix 3. EVIDENCE TABLE

Evidence Table : Safety

**Question: Is insulin pump therapy safe to be used in diabetes patients?**

| Bibliographic citation | Study Type / Methodology | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up | Outcome measures/ Effect size | General comments |
|---|---|---|---|---|---|---|---|---|
| 1. Colquitt JL, Green C, sidhu MK, Hartwell D, Waugh N. Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes. Health Technol Assess 2004;9(43). | Health technology assessment from the sources of information from year 1980 to 2002. Twenty studies comparing CSII with MDI were identified. These included eight parallel RCTs. Nine randomised crossover studies and three non-random crossover studies. | I | Twenty studies comparing CSII with MDI. These included eight parallel RCTs, nine randomised crossover studies and three non-random crossover studies. Fourteen studies included adults with Type I diabete, four studies included pregnant women and two studies included adolescents. | CSII using insulin pumps compared with optimized MDI( at least three injections per day). Analogue compared with soluble insulin in CSII. | MDI | 8 weeks to 60 months | Hypoglycaemic events did not differ significantly between CSII and MDI in most trials, but some found fewer events with CSII and one found more hypoglycaemia and hypoglycaemia coma with CSII. | |

Evidence Table : Safety

**Question: Is insulin pump therapy safe to be used in diabetes patients?**

| Bibliographic citation | Study Type / Methodology | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up | Outcome measures/ Effect size | General comments |
|---|---|---|---|---|---|---|---|---|
| 2.Côté B, St-Hilaire C. Comparison of the insulin pump and multiple daily insulin injections in intensive therapy for type 1 diabetes. Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS). 2005; xv-83 p. | Health Technology Assessment with articles and abstracts published in English, French, Spanish, Italian and German between January 2002 and July 2004 were selected. Articles of randomized, controlled trials, randomized cross-over trials, cohort and case series of at least 10 weeks' duration were included for the assessment. | I | Of the 341 articles and other publications identified, 178 were included. After they were read, 56 studies (25 adult and 31 pediatric), two recent meta-analyses and four economic analyses were selected | Insulin pump | Multiple Daily Insulin Injections using NPH and glargine. | | Safety is evaluated in terms of mortality and severe hypoglycamic episodes and ketoacidosis episodes due to pump malfunction.<br><br>Randomized, controlled trials have found no difference, in childrens or adults, in the incidence of severe hypoglycemic episodes with the pump compared to multiple injections.<br><br>Nonrandomized studies have reported fewer severe hypoglycemic episodes in pump-treated patients, but this can be explained by the choice of subjects in such studies, where pump therapy is offered to those patients who are most likely to benefit from it.<br><br>Two nonrandomized studies, one involving adults selected at the beginning of the study, the other involving children, found that pump therapy and multiple injections with glargine are more effective than multiple injections with NPH in reducing the incidence of severe hypoglycemic episodes.<br><br>As for the incidence of ketoacidotic episodes, studies have found no significant difference between pump therapy and multiple injections, although the absolute number of ketoacidosis episodes is higher with the pump. | |

Evidence Table : Safety

**Question: Is insulin pump therapy safe to be used in diabetes patients?**

| Bibliographic citation | Study Type / Methodology | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up | Outcome measures/ Effect size | General comments |
|---|---|---|---|---|---|---|---|---|
| 3. Reznik Y, Cohen O,Aronson R et al. Insulin pump injections for treatment of type 2 diabetes (OpT2mise): a randomized open-label controlled trial. Lancet 2014;384:1265-72. | Randomised Controlled Trial.<br><br>Multicentre, controlled trial with 331 randomly assigned type 2 diabetes patients to insulin pump treatment and multiple daily injection group. | I | 331 patients randomly assigned (168 to pump treatment , 163 to multiple daily injections). Mean glycated haemoglobin at baseline was 9% (75mmol/mol) in both group. | Insulin pump treatment group | Multiple daily injection group | 6-month | 5 episodes of hyperglycaemia related to device or study procedure in pump treatment group, which did not result in hospital admission.<br><br>Three diabetes-related serious adverse events (hyperglycaemia or ketosis without acidosis) resulting in admission to hospital occurred (two in the pump treatment group, one in the multiple daily injection group).<br><br>No episodes of ketoacidosis occurred in either group during the study.<br><br>One episode of severe hypoglycaemia occurred in the multiple daily injection groups, in a female developed confusion and had a blood glucose concentration of 1.7mmol/L. | |

Evidence Table : Safety

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| Bibliographic citation | Study Type / Methodology | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up | Outcome measures/ Effect size | General comments |
|---|---|---|---|---|---|---|---|---|
| 4. Campbell S, Suebwongpat A, Standfield L et al. Systematic review update and economic evaluation for the New Zealand setting: Subcutaneous insulin pump therapy. HSAC Report 2008; 1(3). | Systematic Review.<br><br>Articles search using Medline and Embase were limited to English-language material published from January 2002 to August 2007 inclusive. Relevant publications were briefly reviewed to inform a qualitative discussion of the incremental costs and outcomes likely to be associated with CSII relative to MDI | I | 726 potentially relevant publications were identified and after consideration of titles and abstracts using the pre-defined study selection criteria, 32 full papers were retrieved and scrutinised in detail for possible inclusion in the review. As a result 12 publications, referring to 11 randomised trials, were ultimately included in the review. | Insulin Pump | Optimised Multiple Daily Injections (MDI) | | <u>Safety</u><br>In adults with type 1 diabetes, episodes of severe hypoglycaemia were infrequent in both trials but were consistently lower during treatment with CSII compared with MDI.<br><br>Ketoacidosis events were also uncommon but occurred more frequently during treatment with CSII than MDI.<br><br>In children and/or adolescents with type 1 diabetes, all three trials reported that episodes of severe hypoglycaemia were less frequent during treatment with CSII compared with MDI.<br><br>Ketoacidosis events were uncommon with both treatment modalities and therefore no firm conclusions can be drawn.<br><br>In adults with type 2 diabetes, the total number of severe hypoglycaemic episodes across the four trials was higher in patients treated with MDI; however, this was driven by only one trial. Two of the trials reported no cases of severe hypoglycaemia and one trial reported more episodes in during treatment with CSII.<br><br>There was insufficient evidence to draw any conclusions regarding the effect of the treatment on the incidences of ketoacidosis. | |

Evidence Table : Safety

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| Bibliographic citation | Study Type / Methodology | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up | Outcome measures/ Effect size | General comments |
|---|---|---|---|---|---|---|---|---|
| 5. Bergenstal RM, Andrew WV et al. Effectiveness of sensor-augmented insulin-pump therapy in Type 1 Diabetes | 1-year, multicenter, randomized, controlled trial compared the efficacy of sensor-augmented pump therapy with MDI. | I | 443 patients randomly assigned (224 to sensor-augmented pump, 219 multiple daily injection).<br><br>Mean glycated haemoglobin baseline was 8.3% in the two study groups. | Sensor-augmented pump | Multiple daily injection group | 1-year | Rates of severe hypoglycaemia and diabetic ketoacidosis were similar in the two study groups.<br><br>There were two hospital admissions in the pump-therapy group for cellulitis related to insertion-site infections and one death from sudden cardiac arrest in a patient in the injection-therapy group who has a history of cardiovascular disease | |

Evidence Table : Safety

**Question: Is insulin pump therapy safe to be used in diabetes patients?**

| Bibliographic citation | Study Type / Methodology | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up | Outcome measures/ Effect size | General comments |
|---|---|---|---|---|---|---|---|---|
| 6. Farrar D, Tuffnell DJ, West J. Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD005542. DOI: 10.1002/14651858.CD005542.pub2. | Cochrane Review with published and unpublished randomized trials comparing CSII with MDI of insulin for pregnant women with diabetes. Quasi-randomised trials were excluded. | I | Five trials with 153 women and 154 pregnancies were included. | Insulin Pump | Multiple Dose Insulin Injection (MDI) | Not available | There were no significant differences in maternal hypoglycaemia (RR 3.00, 95% CI 0.35 to 25.87) in two trials and 61 pregnancies.<br><br>There were no significant differences in maternal hyperglycaemia (RR 7.00, 95% CI 0.39 to 125.44) in two trials and 61 pregnancies. | |

Evidence Table : Efficacy /Effectiveness

**Question: Is insulin pump therapy effective in diabetes patients?**

| Bibliographic citation | Study Type / Methodology | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up | Outcome measures/ Effect size | General comments |
|---|---|---|---|---|---|---|---|---|
| 1. Colquitt JL, Green C, sidhu MK, Hartwell D, Waugh N. Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes. Health Technol Assess 2004;9(43). | Health technology assessment from the sources of information from year 1980 to 2002. Twenty studies comparing CSII with MDI were identified. These included eight parallel RCTs, nine randomised crossover studies and three non-random crossover studies. Nine randomised crossover studies and three non-random crossover studies. | I | Twenty studies comparing CSII with MDI. These included eight parallel RCTs, nine randomised crossover studies and three non-random crossover studies. Fourteen studies included adults with Type I diabetes, four studies included pregnant women and two studies included adolescents. | CSII using insulin pumps compared with optimized MDI( at least three injections per day). Analogue compared with soluble insulin in CSII. | MDI | 8 weeks to 60 months | <u>Adults with Type I diabetes</u><br>Mean improvement in glycated haemoglobin of about 0.6% was found with CSII compared with MDI in both short-term [-0.64, 95% CI -1.28 to 0.01] and longer term (-0.61, 95%CI -1.29 to 0.07) studies.<br><u>Pregnancy</u><br>Three studies found no difference in glycated haemoglobin between CSII and MDI. Less insulin per KG was required by patients with CSII in one study, but two other studies found no significant difference. Patient preference and quality of life were not reported.<br><u>Adolescents</u><br>One study found no significant difference between CSII and MDI, whereas the second study found lower glycated haemoglobin and insulin dose with CSII. Over half of the patients chose to continue treatment with CSII in the former study.<br><u>Children</u><br>No randomised trials were identified. Case series suggest that CSII has a place in treatment of children with diabetes, but this needs to be confirmed in randomised studies.<br><u>Short-term use in adults with poorly controlled Type 2 diabetes</u><br>It has been suggested that short-term CSII may help in patients with Type 2 diabetes on high doses of oral drugs and who are resistant to insulin. No good evidence was found. | |

Evidence Table : Efficacy /Effectiveness

**Question: Is insulin pump therapy effective in diabetes patients?**

| Bibliographic citation | Study Type / Methodology | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up | Outcome measures/ Effect size | General comments |
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| 2. Côté B, St-Hilaire C. Comparison of the insulin pump and multiple daily insulin injections in intensive therapy for type 1 diabetes. Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS). 2005; xv-83 p. | Health technology assessment with selected articles and abstracts published in English, French, Spanish, Italian and German between January 2002 and July 2004 were selected.<br>Articles of randomized, controlled trials, randomized cross-over trials, cohort and case series of at least 10 weeks' duration were included for the assessment. | I | Of the 341 articles and other publications identified, 178 were included. After they were read, 56 studies (25 adult and 31 pediatric), two recent meta-analyses and four economic analyses were selected | Insulin pump | Multiple Daily Insulin Injections using NPH and glargine. | | Efficacy<br><u>Comparison of pump therapy and multiple injections with NPH</u><br>For adult diabetic, pump therapy can lead to a modest improvement in glycemic control (mean decrease of 0.51 to 0.6% in the HbA1c level)<br><br>For diabetic children, randomized, controlled trials have not found the pump to have any advantage over multiple injections with NPH.<br><br>For patients selected because of inadequate glycemic control (HbA1c level ≥ 8.5%), one randomized, controlled trial noted a greater improvement with the pump in the adults (0.84% decrease in the HbA1c level).<br><br><u>Comparison of pump therapy and multiple injections with glargine</u><br>For adults, the pump is as effective as multiple injections with glargine in terms of glycemic control.<br><br><u>Quality of life</u><br>The data on the impact of the pump on quality of life from randomized or cohort studies involving the general population of type 1 diabetics do not indicate any improvement.<br><br>In adult patients selected because of inadequate glycemic control, two studies report the pump led to a significant improvement in various aspects of quality of life.<br><br>For children, randomized, controlled trials report no significant effect on the quality of life of children who use the pump. Only one such trial found a tendency in favour of pump therapy with regard to certain domains covered by the DQOLY questionnaire, particularly satisfaction with the treatment. | |

Evidence Table : Efficacy /Effectiveness

**Question: Is insulin pump therapy effective in diabetes patients?**

| Bibliographic citation | Study Type / Methodology | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up | Outcome measures/ Effect size | General comments |
|---|---|---|---|---|---|---|---|---|
| 3.Cummins E, Royle P, Snaith A et al. Clinical and cost-effectiveness of continous subcutaneous infusion for diabetes: updating review. The Aberdeen HTA group. 2004;8(43). | Health Technology Assessment with the searches of electronic databases including Medline, Embase, Science Citation Index, Cocharane Library from year 2002 to June 2007 were done. | I | 74 studies retained for data extraction and inclusion for clinical effectiveness. 8 RCTs of CSII vs best MDI in T1 and T2DM. 8 RCTs of CSII vs NPH in T1DM. 48 observational studies of CSII. 6 studies of pump in pregnancy. 4 systematic reviews. | Insulin pump | Multiple Dose Insulin (MDI) injections | | For type I diabetes patients, few trials have been done, most are very small, and only two have been published in full, one of which was only a pilot.<br><br>For type II diabetes patients, there was little evidence that CSII was better than analogue based MDI. In one study, a clinically significant difference in HbA1c was reported but if failed to reach statistical significance. The Berthe 2007 trial showed that CSII was better than NPH-based MDI.<br><br>For children and adolescents, one trial (Doyle 2004) reports that HbA1c is significantly lower on CSII than on analoque-based MDI. The other studies in adults report no differences in HbA1c. | |

Evidence Table : Efficacy /Effectiveness

**Question: Is insulin pump therapy effective in diabetes patients?**

| Bibliographic citation | Study Type / Methodology | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up | Outcome measures/ Effect size | General comments |
|---|---|---|---|---|---|---|---|---|
| 4. Campbell S, Suebwongpat A, Standfield L, Weston A. Systematic review update and economic evaluation for the New Zealand setting: Subcutaneous insulin pump therapy. HSAC Report 2008; 1(3). | Systematic Review with articles search using Medline and Embase were limited to English-language material published from January 2002 to August 2007 inclusive. Relevant publications were briefly reviewed to inform a qualitative discussion of the incremental costs and outcomes likely to be associated with CSII relative to MDI | I | 726 potentially relevant publications were identified and after consideration of titles and abstracts using the pre-defined study selection criteria, 32 full papers were retrieved and scrutinised in detail for possible inclusion in the review. As a result 12 publications, referring to 11 randomised trials, were ultimately included in the review. | CSII | Optimised Multiple Daily Injections (MDI) | | <u>Efficacy</u><br>In trials of adults with type 1 diabetes, therapy with CSII was associated with a greater reduction in HbA1c levels compared with MDI, at all time points examined (4, 6 and 8 months). Although the publications reported a statistically significance difference between CSII and MDI in terms of endpoint HbA1c levels, meta-analysis of baseline adjusted data from the two trials at a common time point (four months) favoured CSII but failed to reach statistical significance.<br><br>Quality of life endpoints were poorly reported but indicate that treatment with CSII may be associated with significantly improved quality of life compared with MDI.<br><br>In children and/or adolescents with type 1 diabetes, HbA1c levels were lower at endpoint after CSII than MDI, although the magnitude of the difference was small.<br><br>Meta-analysis of baseline adjusted data at a common time point (3-4 months) confirmed the trend in favour of CSII but did not reveal a significance difference between treatment modalities in terms of HbA1c levels at endpoint.<br><br>Quality of life was assessed in all three trials using a youth-specific questionnaire. Whilst two studies found no statistically significant difference between CSII and MDI, the third reported a significant difference in favour of CSII in the satisfaction subscale ($P<0.05$), but not other subscales.<br><br>In adults with type 2 diabetes, the change from baseline in HbA1c levels was greater with CSII than MDI.<br><br>Meta-analysis of data from the four trials (using the longest time point in each trial) confirmed the trend favour of CSII but the difference was not statistically significant.<br><br>One of the four trials reported quality of life | |

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| | | | | | | | outcomes and showed no difference between treatment modalities.<br><br>Of the two studies that reported the effect of treatment on lipid levels, there was no significant difference between CSII and MDI.<br><br>In pregnant women with diabetes, HbA1c levels were lower in women treated with MDI compared with CSII, in both second and third trimester, but the difference was not significant. | |

Evidence Table : Efficacy /Effectiveness

**Question: Is insulin pump therapy effective in diabetes patients?**

| Bibliographic citation | Study Type / Methodology | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up | Outcome measures/ Effect size | General comments |
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| 5. Misso ML, Egberts KJ, Page M, O'Connor D, Shaw J. Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD005103. DOI: 10.1002/14651858.CD005103.pub2. | Cochrane Review with all published and unpublished randomized and quasi-randomised controlled trials (blind and open, parallel and cross-over) designed to compare people with type 1 diabetes taking insulin in the form of either CSII or MDI. There were no time or language restrictions. The articles searches were done up to 20 July 2009. | I | Twenty three studies randomised 976 participants with type 1 diabetes to either intervention. | Insulin Pump | Multiple insulin injections (three or more insulin injections per day) | Not available | There was a statistically significant difference in glycosylated haemoglobin A1c (HbA1c) favouring CSII (weighted mean difference -0.3% (95% confidence interval -0.1 to -0.4). There were no obvious differences between the interventions for non-severe hypoglycaemia, but severe hypoglycaemia appeared to be reduced in those using CSII. Quality of life measures suggest that CSII is preferred over MI. No significant difference was found for weight. Adverse events were not well reported, no information is available on mortality, morbidity and costs. | |

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| 6. Farrar D, Tuffnell DJ, West J. Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD005542. DOI: 10.1002/14651858.CD005542.pub2. | Cochrane Review with published and unpublished randomized trials comparing CSII with MDI of insulin for pregnant women with diabetes. Quasi-randomised trials were excluded. | I | Five trials with 153 women and 154 pregnancies were included. | Insulin Pump | Multiple Dose Insulin Injection (MDI) | Not available | There was no significant difference in either of the primary outcomes; macrosomia (birthweight greater than 4000 g) (risk ratio (RR) 3.20, 95% confidence interval (CI) 0.14 to 72.62; two trials, 61 pregnancies) and operative birth, caesarean birth being the only outcome reported (RR 1.09, 95% CI 0.66 to 1.77; three trials, 71 pregnancies)<br><br>There was an increase in mean birthweight associated with CSII with MDI of borderline significance (mean difference (MD) 220.56g, 95% CI -2.09g to 443.20g; two trials, 61 pregnancies, P-0.05). However, the large CI and the lack of significant difference in macrosomia rate, suggests uncertainty of effecy and a clinically insignificant difference.<br><br>No significant differences were found in perinatal mortality (RR 2.33, 95% CI, 0.38 to 14.32; three trials, 71 pregnancies), fetal anomaly (RR 1.07, 95% CI, 0.07 to 15.54; two trials 61 pregnancies), maternal hypoglycaemia (RR 3.00, 95% CI 0.35 to 25.87; two trials, 61 pregnancies) or maternal hyperglycaemia (RR 7.00, 95% CI, 0.39 to 125.44; two trials, 61 pregnancies) or small-for-gestational age (average RR 1.40, 95% CI 0.10 to 18.71; two trials, 61 pregnancies, random-effects analysis $T^2 = 1.10$, $I^2 = 31\%$). | |

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| 7. Reznik Y,Cohen O, Aronson R et al. Insulin pump injections for treatment of type 2 diabetes (OpT2mise): a randomized open-label controlled trial. Lancet 2014;384:1265-72. | Randomised Controlled Trial.<br><br>Multicentre, controlled trial with 331 randomly assigned type 2 diabetes patients to insulin pump treatment and multiple daily injection group. | I | 331 patients randomly assigned (168 to pump treatment , 163 to multiple daily injections).<br><br>Mean glycated haemoglobin at baseline was 9% (75mmol/mol) in both groups. | Insulin pump treatment group | Multiple daily injection group | 6-month | The primary endpoint was the between-group difference in change in mean glycated haemoglobin form baseline to the end of the randomised phase.<br>Secondary endpoints included changes from baseline to 6 months of continuous glucose monitoring data, including mean 24-h glucose concentrations, the area under the curve (AUC) for hypoglycaemia (defined as sensor glucose values <3.9mmol/L) and hyperglycaemia (sensor glucose values >10mmol/L), and the time spent in hypoglycaemia and hyperglycaemia.<br><br>Pump treatment group shown decrease in baseline mean glycated haemoglobin (mean change -1.1%, SD 1.2; -12mmol/mol,SD13)<br><br>Multiple daily injection group (-0.4%,SD 1.1; -4mmol/mol, SD12)<br><br>The difference between the 2 groups was -0.7%(95% CI -0.9 to -0.4; -8mmol/mol, 95% CI -10 to -4 mmol/mol, adjusted p<0.0001). | |

Evidence Table : Efficacy /Effectiveness

**Question: Is insulin pump therapy effective in diabetes patients?**

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| 8. Bergenstal RM, Tamborlane WV, Ahmann A et al.Effectiveness of sensor-augmented insulin-pump therapy in Type 1 Diabetes. N Eng J Med 2010; 363(4):311-320. | Patients were randomly assigned to receive either sensor-augmented pump therapy or MDI with the use of a block design, stratified according to age group: adult (19 to 70 years of age) or children (7 to 18 years of age).<br><br>1-year, multicenter, randomised, controlled trial. | I | Patients with type 1 diabetes were eligible if they were between the ages of 7 and 70 years, had received MDI during previous 3 months, had a glycated hemoglobin level between 7.4% and 9.5%.<br><br>443 patients randomly assigned (224 to sensor-augmented pump, 219 multiple daily injection).Mean glycated haemoglobin baseline was 8.3% in the two study groups. | Sensor-augmented pump integrates with continuous glucose monitoring (MiniMed Paradigm REAL-Time System, Metronic) | Multiple daily injection group | 1-year | The baseline mean glycated haemoglobin level (8.3% in the two study groups) had decreased to 7.5% in the pump-therapy group as compared with 8.1% in the injection-therapy group, for a between-group of -0.6 percentage point (95% confidence interval, -0.7 to -0.4; P<0.001). | |

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| Bibliographic citation | Study Type / Methodology | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up | Outcome measures/ Effect size | General comments |
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| 9. Bolli G,Kerr D, Thomas R et al. Comparison of a Multiple daily Insulin Injection Regimen (Basal Once Daily Glargine Plus Mealtime Lispro) and Continuous Subcutaneous Insulin Infusion (Lispro) in Type 1 Diabetes. Diabetes Care 2009:32(7)Pg1170-1176 | Randomised, parallel group, open label, multicenter (n=5) study performed in three European countries with a 1-week run-in period followed by a 24-week treatment period (including 4 weeks of active dose titration), with clinic visits at 0,2,8,16 and 24 weeks and 2 weeks follow-up.<br><br>People with type 1 diabetes on NPH-based insulin therapy were randomized to CSII or glargine-mased MDI and flowed for 24 weeks in an equivalence design. | I | Participants were aged 18-70 years, fasting plasma glucose >7.0 mmol/l, fasting plasma C-peptide <0.10nmol/l.<br><br>Fifty people were randomized and 43 completed the study | Insulin Pump | Multiple Daily Insulin injections | 24 weeks | Mean A1C fell similarly in two groups (CSII -0.7±0.7%; MDI -0.6±0.8%) with a baseline-adjusted difference of -0.1% (95%CI-0.5 to 0.3).<br><br>Total insulin requirement at end point was 36.2±11.5 units/day on CSII and 42.6±15.5 units/day on MDI.<br><br>On CSII, 1,152 hypoglycemia events were recorded by 23 of 28 participants (82%) and 1,022 in the MDI group by 27 of 29 patients (93%)(all hypoglycaemia differences were non-significant).<br><br>Treatment satisfaction score increased more with CSII; however, the change in score was similar for the groups.<br><br>Costs were ~3.9 times higher for CSII. | |

Evidence Table : Efficacy /Effectiveness

**Question: Is insulin pump therapy effective in diabetes patients?**

| Bibliographic Citation | Study Type / Methodology | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up | Outcome measures/ Effect size | General comments |
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| 10. Stephanie RJ, Matthew NC, Timothy W. Jones et al. Long-term outcome of insulin pump therapy in children with type 1 diabetes assessed in a large population-based case-control study. Diabetologia 2013:56(11)pg 2392-2400. | Case-control design matched patients already commenced on insulin pump therapy with patients on injection therapy on the basis of age (within 1 year), duration of diabetes (within 2 years) and HbA1c at the time of pump start (within 1.5%). | II-2 | 345 pump cohort was matched with 345 non-pump cohort. | Insulin pump | Multiple dose injection group | 7 years | The mean difference of HbA1c between the pump and non-pump cohort was 0.6% over the 7 years of follow-up.<br><br>Once on insulin pump therapy, the pump cohort had a significantly improved HbA1c at all time-points (3 months, 12 months, 6 months until 2 years and yearly after), with an initial rapid improvement in the pump vs non-pump groups of 0.6% (6.6mmol/mol) at 3 months ($p<0.001$).<br><br>The level of improvement was lowest at 2 years, although still significant at 0.3% (3.3mmol/mol, $p=0.01$).<br><br>The improvement in the pump cohort increased from years 2 to 7, reaching a maximum of 1.0%(10.9 mmol/mol, $p<0.01$) at 6 years. | |

Evidence Table : Efficacy /Effectiveness

**Question: Is insulin pump therapy effective in diabetes patients?**

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|---|---|---|---|---|---|---|---|---|
| 11. Ooi HL, Wu LL. Insulin pump therapy in children and adolescents with Type 1 Diabetes: improvements in glycemic control and patients' satisfaction – Hospital UKM experience. Medical Journal Malaysia 2011:66(4) pg 308-312 | Retrospective cohort study were done to review 18 patients with type 1 diabetes started on insulin pump therapy between April 2004 and December 2009. | II-2 | 18 type 1 diabetes patients. | Insulin pump | | 5 years | The annual mean HbA1c dropped 0.6% in the first year of pump use (8.1±1.2%) when compared with HbA1c at the start of treatment (8.7±1.5%).<br><br>The value then gradually increased from second year to fourth year of pump use before it dropped again in the fifth and sixth year of treatment.<br><br>However when the differences between the annual mean HbA1c after using pump were compared with HbA1c at the start of treatment, only the differences in the first two years of treatment were statistical significant.<br><br>The differences in mean annual HbA1cin the fifth and sixth year of treatment were not significant despite lower in actual HbA1c value. | |

Evidence Table : Cost/Cost-effectiveness

**Question: Is insulin pump therapy costly/cost-effective to be used in diabetes patients?**

| Bibliographic citation | Study Type / Methodology | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up | Outcome measures/ Effect size | General comments |
|---|---|---|---|---|---|---|---|---|
| 1. Colquitt JL, Green C, sidhu MK, Hartwell D, Waugh N. Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes. Health Technol Assess 2004;9(43). | Health technology assessment from the sources of information from year 1980 to 2002. Twenty studies comparing CSII with MDI were identified. These included eight parallel RCTs. Nine randomised crossover studies and three non-random crossover studies. | I | Twenty studies comparing CSII with MDI. These included eight parallel RCTs, nine randomised crossover studies and three non-random crossover studies. Fourteen studies included adults with Type I diabete, four studies included pregnant women and two studies included adolescents. | CSII using insulin pumps | optimized MDI( at least three injections per day). Analogue compared with soluble insulin in CSII. | | <u>Cost</u> The additional cost of CSII compared with MDI varies according to the make of pump and the estimated life of the device, from £1091 per annum using the cheapest pump and assuming an 8-year life of the pump to £1680 per annum with the most expensive model and assuming a life of only 4 years. | |

Evidence Table : Cost/Cost-effectiveness

**Question: Is insulin pump therapy costly/cost-effective to be used in diabetes patients?**

| Bibliographic citation | Study Type / Methodology | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up | Outcome measures/ Effect size | General comments |
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| 2. Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS). Comparison of the insulin pump and multiple daily insulin injections in intensive therapy for type 1 diabetes. Report prepared by Brigitte Côté and Carole St-Hilaire (AETMIS 04-07). Montréal: AETMIS, 2005, xv-83 p. | Health Technology Assessment.<br><br>Articles and abstracts published in English, French, Spanish, Italian and German between January 2002 and July 2004 were selected. Articles of randomized, controlled trials, randomized cross-over trials, cohort and case series of at least 10 weeks' duration were included for the assessment. | I | Of the 341 articles and other publications identified, 178 were included. After they were read, 56 studies (25 adult and 31 pediatric), two recent meta-analyses and four economic analyses were selected | Insulin pump | Multiple Daily Insulin Injections using NPH and glargine. | | <u>Cost-effectiveness</u><br>Four economic studies comparing insulin pump therapy and multiple injections with NPH were identified, including one published in a scientific journal [Scuffham and Carr, 2003], two in the form of abstracts [Roze et al., 200; Roze and Palmer, 2002] and one as paper presented at a health economists conference [De Sola-Morales et al., 2004]. The characteristics of these studies and their main findings are presented in Table F-1 in Appendix F.<br><br>8-year Markov model Scuffham and Carr [2003] constructed to compare the costs and utility of these two treatment modalities took hypoglycaemic and ketoacidotic apisodes into account. The model showed the incremental cost per QALY (cost/QALY) with the pump was £11,461 (CA$27,736)(Standard deviation: £3,656 (CA$8,848). | |