Original Article DOI: http://doi.org/10.4038/sjdem.v9i1.7294

The 12 month impact of continuous insulin infusion therapy on glycaemic control in adults with type 1 diabetes, at the Townsville hospital, Queensland - A retrospective study.

Suji Prabhaharan, Vasant Shenoy, Kunwarjit Sangla

The Townsville Hospital, Queensland, Australia.

Abstract

Aims: The purpose of this study was to assess the impact of continuous subcutaneous insulin infusion therapy (CSII) on glycosylated haemoglobin level (HbA1c), total daily dose of insulin (TDD), weight, episodes of diabetic ketoacidosis (DKA), severe hypoglycaemia, hospital admissions due to any other causes at 12 months of CSII therapy and to identify the predictive factors for good response to treatment, in patients attending the Townsville hospital diabetes centre.

Methodology: This is a retrospective quality assurance single centre study. A total of 105 type 1 diabetes patients on continuous subcutaneous insulin infusion (CSII) were identified from 1st January 2001 to 31st December 2014 of whom; only 52 patients had sufficient data to be included in the study. The HbA1c, total daily dose of insulin and weight were collected 4 months before, after and at 12 months of CSII therapy. Patients demographic details, variables related to disease, treatment and follow up were also recorded.

Results: Among the 52 patients analysed, 34.6% were males. The base line median HbA1c for females and males were 8.5% and 8.6% respectively. A significant reduction in baseline median HbA1c (8.6%) was noted both at 4 months {0.6%, (p=0.035)} and 12 months {0.7% (p=0.001)} of continuous subcutaneous insulin infusion therapy. The statistically significant reduction in HbA1c at 4 months was maintained at 12 months (p=0.025). At 12 months of CSII therapy a median HbA1c level of 7.7% was noted in those more than thirty years and 8.6% in less than 30 years of age. The median HbA1c was 7.8% in those who had diabetes for more than 10 years and 8% in less than 10 years. There was no difference in the median HbA1c in females (7.8%) and males (7.9%) at 12months of CSII therapy. At 4 months, the greatest reduction in HbA1c (1.1%) was observed in those who had a base line HbA1c of > 10%. A significant reduction in baseline median total daily dose (TDD) of insulin (57 units) noted both at 4 months (29.9 units (p<0.001) and 12 months (25u (p<0.001). There was no significant variation noted in the weight over 12 months.

Conclusions: This study adds to the existing literature that continuous subcutaneous insulin infusion therapy significantly improves glycaemic control, reduced the total daily dose of insulin and had no effect on weight over 12 months. In our study age < 30 years and HbA1c of > 10% prior to commencement of therapy are predictors of poor glycaemic outcome at 12 months. Duration of diabetes and gender did not influence the glycaemic outcomes at 12 months.

Correspondence email: sujiprabhaharan@gmail.com

Introduction

The incidence and prevalence of diabetes continues to rise, with more than 552 million people worldwide expected to be affected by this disorder by 2030 (1).Type 1 diabetes is an autoimmune disease, which requires lifelong insulin treatment for euglycaemia and prevention of complications due to glycaemic variability. Type 1 diabetes most commonly occurs in childhood and adolescence with increasing incidence in older age group (2). In Australia, the prevalence rate is 139 cases per 100,000 population which, places it as the 10th highest among the developed countries (3). Type 1 diabetes causes a massive burden on individuals, the community and the health care system (4). The financial burden of type 1 diabetes is estimated to be $570 million annually in Australia (5).

The corner stone of management of diabetes mellitus is intensive glycaemic control to prevent chronic hyperglycaemia induced microvascular and macrovascular complications. (6,7). The current model of care for most adult type 1 diabetes patients in Australia is multiple daily dose insulin as opposed to continuous subcutaneous insulin infusion therapy due to the financial burden.

Intensive insulin therapy is well proven to reduce micro and macro vascular complications in diabetes (6). However intense therapy is associated with severe hypoglycaemic events (6).

CSII therapy delivers small dose of rapid-acting insulin throughout the day (the basal rate). A bolus dose of insulin is delivered at meal-times and additional boluses can be administered to correct high blood glucose levels. CSII therapy has a number of advanced features that enable them to closely mimic normal pancreatic physiology. According to American Diabetes Association (ADA) guidelines, type 1 diabetic patients with wide glycaemic variability, recurrent diabetic ketoacidosis, frequent hypoglycaemia and hypoglycaemic unawareness are most eligible for CSII therapy (8).

All patients who are eligible for CSII therapy should be proficient in carbohydrate counting and should receive a structured education programme; therefore it is standard practice that patients will be on multiple daily insulin injections prior to initiation of CSII therapy (8).

Multiple studies have looked at the efficacy of continuous subcutaneous insulin infusion (CSII) on glycaemic control and have shown improvement in HbA1c levels compared to MDI (4, 7, and 13). The studies that looked at the long term efficacy of CSII therapy on glycaemic targets also shows CSII therapy is better in both short term and long term glycaemic control compared to MDI (15, 16, 17).

CSII therapy is associated with decreased risk of severe hypoglycaemia and the need for emergency medical care (18, 19). The latter translates into reduction in the cost of care and utilization of health care resources (9). The sensor augmented CSII therapy with automated insulin suspension devices has proven to reduce moderate to severe hypoglycaemic events compared to standard CSII therapy (10).
Quality of life measures have shown improvement with CSII therapy compared with MDI (11). The cost associated with consumables, pump failure, hypoglycaemia, diabetic ketoacidosis, lipohypertrophy and skin infection are recognised disadvantages of CSII therapy (12).

The aim of this study is to assess the glycaemic outcomes, total daily dose of insulin and weight of type 1 diabetes patients on CSII therapy and identify the predictive factors for good response to treatment. This study will provide guidance for efficient and effective patient selection criteria, implementing local guidelines or recommendations for safe and sustainable service and optimise existing patient management.

Methodology

This study is a retrospective quality assurance chart audit conducted at the Townsville hospital diabetes outpatient clinic. According to both inclusion and exclusion criteria a total of 105 patients on CSII therapy were identified from 1st January 2001 to 31st of December 2014. The inclusion criteria were all patients with type 1 diabetes, age more than 18 years and completed minimum of 12 months of CSII therapy at the time of data collection. The exclusion criteria were pregnant women, patients with chronic kidney disease stage 5, end stage liver disease with Child- Pugh score C, discontinuation of CSII therapy in less than 12 months, patients with solid tumours on chemotherapy and organ transplant. Of the 105 patient's, 53 patients had insufficient data even though they met the inclusion criteria. The patients who were excluded due to insufficient data were those who did not have information on HbA1c, weight and total daily dose of insulin for both at 4 and 12 months of CSII therapy. Similarly those who did not have data for number of episodes of diabetic ketoacidosis (DKA), severe hypoglycaemic episodes and hospital admissions due to any causes both at 12 months before and after CSII therapy were excluded. Therefore at the end of data collection only 52 patients had sufficient data to include in the study.

Data were collected from handwritten patient medical records as well as public, private laboratory investigations and point of care testing (POC-A1c). HbA1c, weight and total daily dose (TDD) of insulin were collected before 4 months and at 4 months and 12 months of CSII therapy. Episodes of DKA, severe hypoglycaemic events and number of hospital admissions due to any other causes were collected both before and after 12 months of CSII therapy. We also collected information about age, gender, duration of diabetes, types, duration and complications of CSII therapy. Micro and macrovascular complications data were collected according to International classification of diseases 10th revision, Australian modification (ICD -10 AM). The number of specialist clinic visits, point of care and phone call review with diabetic educators were recorded before and after 4months and 12 months of CSII therapy.

The number of hospital admissions due to DKA or any other causes and severe hypoglycaemic episodes were very few both before and after CSII therapy. Therefore these data were not analysed.

Clinically significant improvement in glycaemic control was defined as a reduction of HbA1c of > or = 0.5% from baseline. Severe hypoglycaemia was defined as events that needed help from a family member, friend or required emergency service or hospital admission.

Given the fact it was a observational study no patients were involved in setting the research question, or outcome measures, nor were they involved in the design or implementation of this study.

Statistics

Descriptive statistics were used for all variables (median, frequencies, and cumulative percentages). Comparison were made using Wilcoxon's signed rank test as these are repeated – measured variables. We considered a P value < 0.05 to be statistically significant and a P value of <0.01 to be highly significant. A subgroup analysis was performed on patients with baseline HbA1c more than 10% and similar statistical analysis methods were used. The data analysis was conducted through SPSS version 22.

Results

A total of 52 patients were analysed in this study. Of the 52, 34.6% were males. The base line characteristics are highlighted in table 1. Both male and female patients were similar in their baseline characteristics. A significant

reduction in baseline median HbA1c (8.6%) was noted both at 4 months {0.6%, (p=0.035)} and 12 months {0.7% (p=0.001)} of continuous subcutaneous insulin infusion therapy (CSII). The statistically significant reduction in HbA1c at 4 months was maintained at 12 months (p=0.025). Only those who had a median HbA1c of > 8% prior to initiation of CSII therapy had HbA1c reduction of >0.5% at 4 months (table 3). The greatest reduction (1.1%) was observed in those who had a base line HbA1c of > 10% (table 3). At 12 months of CSII therapy a reduction in the base line median HbA1c was noted (8.6% to 7.7%) in those more than thirty years but an increase in median HbA1c was noted in those who are less than 30 years (8.0% to 8.6%). The median Hba1c was 7.8% in those with diabetes more than 10 years and 8% in less than 10 years. There was no difference in the median HbA1c in females (7.8%) and males (7.9%) at 12months of CSII therapy.

A significant reduction in baseline median total daily dose (TDD) of insulin (57 units) noted both at 4 months (29.9 units (p<0.001) and 12 months (25units (p<0.001) of CSII therapy. The reduction in total daily dose of insulin at 12 months of CSII was not significant (p=0.07) compared to median total daily dose of insulin at 4 months (fig 2).

No statistically significant change noted in the baseline weight both at 4 months {73.0 kg (p=0.13)} and 12 months {73.5kg (p=0.12)} of continuous subcutaneous insulin infusion therapy (fig 3). There was no significant variation noted in the weight over 12 months..A subgroup analysis was performed on patients with baseline median HbA1c of more than 10%. The base line characteristics of these patients are highlighted in table 2. A statistically significant reduction in median HbA1c (11.1%) was noted both at 4 months {1.1%, (p=0.025)} and 12 months {1.1%, (p=0.01)} of CSII therapy (fig 4). The reduction in HbA1c from 4 months to 12 months was not statistically significant {0%, (p=0.262).

Table 1: Baseline characteristics of the study population (n=52)

Variable (median)	Male	Female
Age (years)	31	29
Duration of diabetes (years)	12	12
HbA1c (%)	8.6	8.5
Weight (kg)	73	73
Total daily dose of insulin (units)	57	57.5

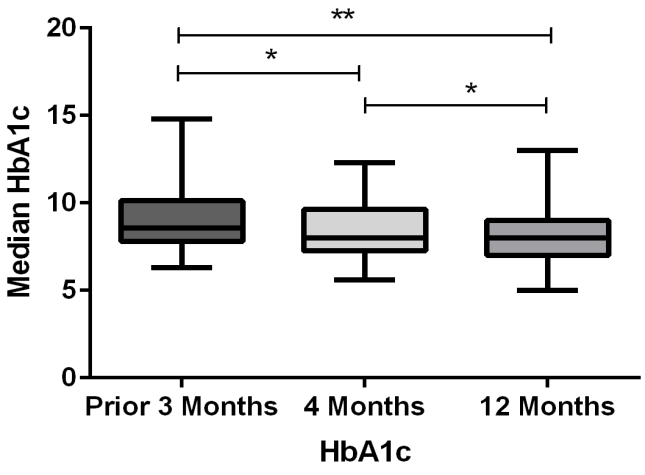

Figure 1: Median HbA1c with duration of CSII therapy

** P value <0.01
* P value <0.05.
CSII- continous subcutaneous insuin infusion

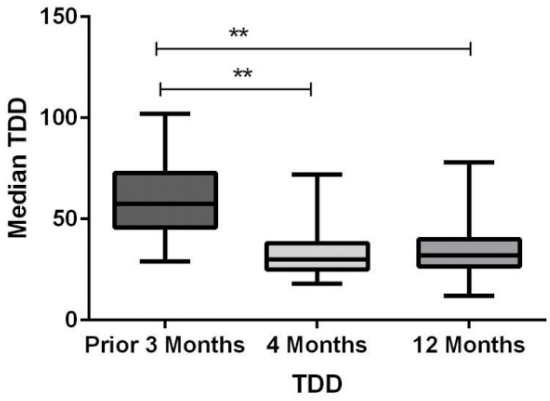

Figure 2: Median total daily dose of insulin with duration of CSII therapy

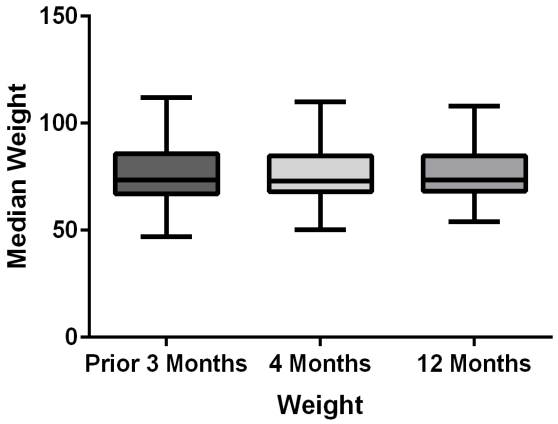

Figure 3: Median weight and duration of CSII therapy

** P value <0.01
* P value <0.05
TDD- total daily dose of insulin.
CSII – continuous subcutaneous insulin infusion

Table 2: Base line characteristics of patients with HbA1c >10% (n=13)

Variable (median)	female	Male
Sex	9	4
Age (years)	22	22
Duration of diabetes (years)	11	7.5
HbA1c (%)	11.1	10.7
Weight (Kg)	70	59
Total daily dose of insulin (units)	68	83.5

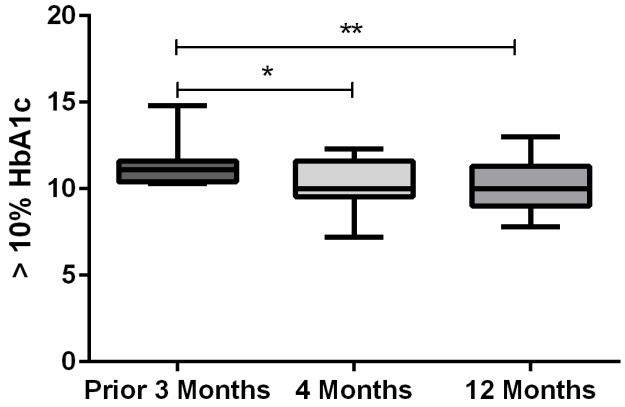

Figure 4: Median HbA1c with duration of CSII therapy in patients with baseline HbA1c >10%.

* P value <0.05.
** P value <0.01
CSII- continous subcutaneous insuin infusion

Table 3: Reduction in median HbA1c after CSII therapy

(HbA1C)	Baseline median HbA1c	Median HbA1c at 4 months of CSII	Median HbA1c at 12 months of CSII
<7%	6.8%	6.7%	6.9%
7.1% – 7.9%	7.7%	7.4%	7.7%
8% – 8.9%	8.4%	7.9%	7.6%
9% – 9.9%	9.3%	8.7%	8.0%
> 10%	11.1%	10%	10%

CSII- continuous subcutaneous insulin infusion

Discussion

In accordance with previous studies (4, 7, 13) our study also demonstrated a statistically significant reduction in the median HbA1c following CSII therapy. The reduction in median HbA1c at 4 months was regardless of the HbA1c prior to CSII therapy (table 3). Clinically significant reduction was observed both at 4 months (0.6%) and 12 months (0.7%) of continuous subcutaneous insulin infusion

therapy. However the reduction in HbA1c was clinically insignificant (0.1%) from 4 to 12 months.

The Diabetes Control and Complication Trial (DCCT) demonstrated a decrease in HbA1c by 0.5% reduced long term micro vascular complications (7). According to American Diabetes Association guidelines (26) , adhereing to a strict follow up protocol both at intiation and continuation phase of of CSII therapy is important for good glycaemic outcomes.

Even though the greatest reduction in HbA1c at 4 months (1.1%) was observed in a subgroup of patients with HbA1c >10% prior to CSII therapy, the median HbA1c remained the same both at 4 and 12 months (10%). These patients median duration of diabetes and age were noted to be less than the rest of the study population (table 2). In consistent with previous studies the transition period from adolescents to younger adults is associated with poor glycaemic control (16, 21). Those who had excellent HbA1c (<7%) while on multiple daily dose regimen and opted for CSII therapy due to life style reasons maintained a HbA1c of < 7% at 1 year. Thus it appears CSII therapy facilitates to maintain better glycaemic control but does not change the pre-existing disease management behaviour.

In this study the baseline HbA1c prior to continuous subcutaneous insulin infusion therapy is a predictor of long term glycaemic control (table 3). This is likely that pre-existing risk factors that have led to the poor glycaemic control could have continued after initiation of CSII therapy.

Our study demonstrates that age less than 30 years and HbA1c of > 10% at base line associated with poor glycaemic targets at 12 months but there was no association between glycaemic outcomes and the duration of diabetes and gender.

In terms of total daily dose of insulin (TDD), our study results were concordant with multiple previous studies. A significant reduction in total daily dose of insulin noted both at 4 and 12 months of CSII therapy compared to multiple daily dose of insulin (4, 6, 17, 25, and 28). The reduction in total daily dose (TDD) of insulin was not statistically significant at 12 months compared to 4 months of CSII therapy, however the reduction was clinically significant. The initial reduction in the total daily dose of insulin could be related to close monitoring and follow up during the intense period of CSII therapy.

Insulin causes weight gain through multiple mechanisms (23). A small case control study on adolescents type 1 diabetes, demonstrated that CSII therapy itself does not usually leads to weight gain and reinforced the importance of education on calorie content and eating habits. (19).

Multiple studies have shown there is no significant difference in weight while on CSII therapy when compared to multiple daily dose of insulin (13, 18, and 25). In accordance with previous studies we also noted a stable weight throughout the 1 year period. The reasons for weight gain with insulin therapy are either due to higher doses or frequent hypoglycaemia (26). In our study, we did not observe weight loss with reduced total daily dose of insulin. Since we did not have data on confounding variables such as calorie intake, appetite and level of exercise, the stable weight could be due to lifestyle factors. However frequent CSII therapy education sessions also have had an impact.

The number of hospital admissions from diabetic ketoacidosis (DKA) and due to any other causes to the Townsville hospital were few. Under reporting or inaccurate coding could have led to few numbers both before and after CSII. Hypoglycaemic events may be under recorded and under reported by patients in clinics. This is mainly due to lack of patient's adherence to glycaemic monitoring. In addition, every patient's indications for CSII therapy or their hypoglycaemic awareness were not available. The evidence is variable with regards to impact of CSII therapy on hypoglycaemic events (6, 18, and 19).

Implications and recommendations

Continuous subcutaneous insulin infusion therapy is an estabilished effective mode of treatment for type 1 diabetes. Our study adds to the existing literature that 12 months of CSII therapy significantly improves glycaemic control, reduced the total daily dose of insulin and had no effect on weight. Even though CSII therapy is an established treatment, it may not be the effective treatment for all.

We did not identify the exact indications for continuous subcutaneous insulin infusion therapy in our study population due to lack of documentation. However about 13.5% of patients had HbA1c less than 7% before CSII. Even though these patients had satisfactory glycaemic control on multiple dose of insulin, they may have opted for CSII therapy for life style reasons. In these patients regardless of the mode of therapy the glycaemic targets remained well within the acceptable range.

A subgroup of patients with HbA1c more than 10% while on multiple dose insulin therapy (MDI), still had a median HbA1c of 10% both at 4 and 12 months of CSII. In this group, mode of treatment did not change the underlying patient disease management behaviour and hence the treatment targets. In Australia CSII therapy is not provided through Medicare, adult patient's eligible for CSII needs private health insurance and this can lead to selection bias (31). Therefore, socioeconomic status becomes one of the most important determinants for CSII therapy rather than the standard indications as described in American Diabetes Association (ADA) guidelines (8).

According to Australian institute of health and welfare CSII therapy was more prevalent in high socioeconomic status due to the cost associated with devices and consumables. High socioeconomic status patients with type 1 diabetes achieve better glycaemic control than low economic status patients (32,33). Hence in our study the patients would have achieved a good glycaemic control regardless of the mode of therapy. Therefore the improvement in glycaemic targets could have been an expected outcome. Hence the results cannot be generalised to all type 1 diabetes patients attending the diabetes centre.

Eventhough there was clinically significant reduction in HbA1c at both 4 and 12 months of CSII therapy the reduction in HbA1c from 4 months to 12 months was clinically insignificant. This may be due to less number of

educational sessions, clinic appointments and lack of motivation from patients after the intial phase of treatment.

As the study did not show a HbA1c reduction from 4 months to 12 months periord, we identified the need to intensify structured educational sessions and follow up after 4 months therapy. There is a necessity to develop better selection criteria to enroll patients for CSII therapy with consideration given to exsisting patient disease management behaviour.

The current exsisiting model of care includes, phone call review by the diabetic educators and specialists clinic appointments. The follow up appointments can be very demanding both during the intiation and continuation phase of CSII therapy with the exsisting resource.

Defined protocols for an effective follow up will minimise resource exhaustion. Group education instead of individual sessions are effcient way to manage time. Treatment goals and follow up frequency needs to be discussed with patients at the beginning of therapy to ensure adherence. An after hours on call system involving the diabetic educators or a clinical nurse practitoner will enhance patient contact with health care system in a timely manner. Nurse practitioner lead clinics to rural and remote areas through tele health service will reduce patient travel time. This will enhance followup and improve glycaemic outcomes.

Maintaining a database helps to identfy patients who are not achieving desired glycaemic targets. This will allow critical appraisal of clinical benefit and cost effectiveness of CSII therapy both at the patient and instituional level. This data also can be used for future prospective larger studies.

The strengths and limitations

This is a single centre study, thus all enrolled patients were under the same care model. This is the first study in North Queensland to ascertain the impact of CSII therapy in type 1 diabetes. Each patient serves as their own control, since their previous insulin regimen was multiple dose insulin therapy.

It is a retrospective, single centre, observational study therefore it is difficult to generalise the outcome to all type 1 diabetes patients attending the outpatient. The HbA1c levels were analysed through both public and private laboratories and point of care testing (POC-A1c). HbA1c levels obtained from point of care testing are lower than laboratory testing (34). The lack of standardization of HbA1c is a limitation in our study.

The CSII technology had advance with time to improve glycaemic outcomes. The advanced devices have been shown to improve both pre-prandial glycaemic control and overnight hypoglycaemia (35). Hence the difference in CSII devices among patients is a limitation in our study.

A significant change in diabetes care came with the development of continuous glucose monitoring system (CGMS). It is an indwelling subcutaneous sensor that check the interstitial fluid glucose readings every 3 to 5 min. CGMS identifies glycaemic excursions and hypoglycaemia over 24 hours and helps to improve both hyper and hypoglycaemia (36). The in- cooperation of (CGMS) in some patients, over the study period, could have contributed to better glycaemic outcomes.
Chronic anaemia due to any reason can falsely reduce the HbA1c level. We did not exclude patients with anaemia apart from those with end stage renal disease. The number of DKA, hospital admissions due to any cause and severe hypoglycaemic events were very small, hence unable to ascertain the impact of CSII therapy on these variables.

Conclusion

This study adds to the existing literature that CSII therapy significantly improves glycaemic control, reduced the total daily dose of insulin and had no effect on weight over 12 months. Our study identifies age less than 30 years and HbA1c of > 10% at base line are predictors of poor glycaemic control at 12 months. Duration of diabetes and gender did not influence the glycaemic outcome. This study identifies the need for defined eligibility criteria for CSII therapy and the need for intense follow up and education beyond 4 months. We did not objectively look at the patient disease management behaviour which is one of the important predictors of glycaemic outcomes. A prospective quality assurance study is needed to reanalyse the outcomes once recommendations are implemented.

References

1. Whiting DR, Guariguata L, Weil C, Shaw J: IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Research and Clinical Practise.* 2011, **94**: 311-321.
2. Incidence of type 1 diabetes in Australia 2000–2013, Australian institute of health and welfare (AIHW).
3. Prevalence of type 1 diabetes among children aged 0–14 in Australia 2013. Australian institute of health and welfare (AIHW).
4. Jhonson SR, Cooper MN, Timothy WJ, Davis EA. Long-term outcome of insulin pump therapy in children with type 1 Diabetes Mellitus assessed in a large population based case control study. *Diabetologica* 2013; **56**:2392–2400.
5. Colagiuri S, Brnabic A, Gomez M, Fitzgerald B, Buckley A, Colagiuri R: DiabCo$t Australia type 1: assessing the burden of type 1 diabetes in Australia. 2009, Canberra: Diabetes Australia.
6. Jay SS, DCCT: The study that forever changed the nature of treatment of type 1 diabetes, *British Journal of Diabetes and Vascular Disease.* 2004; **4**(1).
7. The Diabetes and Complications Trial/Epidemiology of Diabetes interventions and complications (DCCT/EDIC) Study Research group. *N Engl. J. Med.***353**, 2643-2653 (2005).

8. American association of clinical endocrinologists/American collage of endocrinologists, consensus statement, *Endocrine practice*, volume **20**, number 5, May 2014.
9. Cummins E et al. Clinical effectiveness and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes: systematic review and economic evaluation. *Health Technol Assessment*. 2010 Feb; 14.
10. Ly. T.T et.al. Effect of Sensor-Augmented Insulin Pump Therapy and Automated Insulin Suspension vs Standard Insulin Pump Therapy on Hypoglycemia in Patients with Type 1 Diabetes a Randomized Clinical Trial. *JAMA*, 2013 Sep 25; **Vol. 310 (12)**, pp. 1240-7.
11. Hoogma RP et al. Comparison of the effects of continuous subcutaneous insulin infusion (CSII) and NPH-based multiple daily insulin injections (MDI) on glycaemic control and quality of life: results of the 5-nations trial. *Diabetes Medicine*. 2006 Feb; **23(2)**:141-7.
12. Banshi D. Saboo et.al. Continuous subcutaneous insulin infusion: practical issues. *Indian journal of Endocrinology and Metabolism*, 2012 Dec; **16**: S259–S262.
13. Misso ML, Egbert's 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.
14. Sherr J, Tamborlane WV.Past present and future of insulin pump therapy: A better shot at diabetes control. *Mt Sinai J Med.* **75**, 352-361 (2008).
15. Selam JL. Evolution of diabetes insulin delivery devices. . *J Diabetes Science and Technology. 2010*; **4(3)**:505-513.
16. Christine J. Orr, MD, Wilma Hopman, PhD, Joy L. Yen, and Robyn L. Houlden, MD. Long-term efficacy of insulin pump therapy on glycaemic control in adults with type 1 diabetes mellitus *Diabetes Technology and Therapeutics*. **volume 17**, number 1, 2015.
17. Carlsson et al. Insulin Pump—Long-Term Effects on Glycaemic Control: An Observational Study at *Diabetes Clinics in Sweden, Diabetes Technology & Therapeutics*. April 2013, **15(4)**: 302-307.
18. Jillweissberg-Benchell, Jeanne Antisdel- Lomaglio, Seshadri R PHD. Meta-analysis of insulin pump therapy. *Diabetes Care*, **26**, 1079-1089 (2003).
19. Melidonis Andreas, Kamaratos Alexandros, Angelidi Angeliki, Thomakos Petros, Vrakas Spiridon, Bakalis John, Fousteris Evangelos, and Iraklianou Stella. The Impact of Continuous Subcutaneous Insulin Infusion Therapy on Efficacy and Safety in a Cohort of Type 1 Diabetes Patients: A 3-Year Prospective Study, *Diabetes Technology & Therapeutics*. March 2016, **18(3)**: 159-163.
20. Pickup JC, Sutton AJ et al. Severe hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. *Diabetes Medicine*. 2008 Jul; **25(7)**:765-74.
21. Tamborlane WV, Beck RW, Bode BW, Buckingham B, Chase HP, et al. (2008) Continuous glucose monitoring and intensive treatment of type 1 diabetes. *The New England Journal of Medicine*. 2008; **359**: 1464–1476.
22. Jane L. Chiang et.al. Type 1 diabetes through the life span: A position statement of the American Diabetes Association. *Diabetes Care*, 2014; **37**:2034–2054.
23. A.N Jacob et al. Potential causes of weight gain in type 1 DM. *Diabetes, Obesity and Metabolism*, **8**, 2006; 404–411.
24. Raile K, Noelle V, Landgraf R, Schwarz HP. Weight in adolescents with type 1 diabetes mellitus during continuous subcutaneous insulin infusion (CSII) therapy. *Journal of Paediatric Endocrinology and Metabolism*. 2002 May; **15(5)**:607-12.
25. Stephen ND, Davis SN, Horton ES, Battelino T, Rubin RR, Schulman KA, Tamborlane WV. Star 3 randomized controlled trial to compare sensor augmented insulin pump therapy with multiple daily injections in the treatment of type 1 Diabetes Mellitus. *Diabetes Technology and Therapeutics* ,**12**, 249-255 (2010).
26. Mc Nay EC, Teske JA, Kotz CM et al. Long-term, intermittent, insulin-induced hypoglycaemia produces marked obesity without hyperphagia or insulin resistance: A model for weight gain with intensive insulin therapy, *American Journal of Physiology Endocrinology and Metabolism*. 2013 January **15**; 304(2).
27. Doyle EA, Weinzimer SA, Steffen AT, Ahern JAH, Vincent M, Tamborlane WV. A randomized prospective trial comparing the efficacy of CSII with MDI using insulin Glargine. , *Diabetes Care* **27,** 1554-1558 (2004).
28. Bergenstal RM, Tamborlane WV, Ahmann A et al. Effectiveness of sensor augmented insulin pump therapy in Type 1 Diabetes mellitus. *N Engl. J Med.* **363**,311-320 (2010).
29. Mitra M. Fatourechi et. al. Hypoglycaemia with Intensive Insulin Therapy: A Systematic Review and Meta-Analyses of Randomized Trials of Continuous Subcutaneous Insulin Infusion versus Multiple Daily Injections. *Journal of Clinical Endocrinology and Metabolism*, March 2009, **94(3)**:729 –740.
30. Jhon Pickup et al. Continuous Subcutaneous Insulin Infusion at 25 years, evidence base for the expanding use of insulin pump therapy in type 1 DM. *Diabetes care*, volume **25**, number 3, March 2002.
31. Insulin pump use in Australia, diabetes series number 18, Australian institute of health and welfare 2012.
32. Ismail IS, Nazaimoon WM, Mohamad WB, Letchuman R, Singaraveloo M, Pendek R, et al. Sociodemographic determinants of glycaemic control in young diabetic patients in peninsular Malaysia. *Diabetes research and clinical practice*. 2000;**47(1)**:57-69.
33. Secrest, Aaron M et al. "Association of Socioeconomic Status with Mortality in Type 1 Diabetes: The Pittsburgh Epidemiology of Diabetes Complications (EDC) Study." *Annals of epidemiology* 21.5 (2011): 367–373.
34. Viviane Leca et al. Point-of-Care Measurements of HbA_{1c}: Simplicity Does Not Mean Laxity with Controls. *Diabetes Care* 2012 Dec; **35(12)**: e85-e85.
35. Catargi B et al. A randomized study comparing blood glucose control and risk of severe hypoglycemia achieved by non-programmable versus programmable external insulin pumps. *Diabetes Metabolism*. 2001 Jun; **27(3)**:323-7.
36. Tanenberg R., Bode B., Lane W., Levetan C., Mestman J., Harmel A.P., Tobian J., Gross T., Mastrototaro J. Use of the Continuous Glucose Monitoring System to guide therapy in patients with insulin-treated diabetes: A randomized controlled trial. *Mayo Clinic. Proceedings*. 2004; **79**:1521–1526.