

ORIGINAL ARTICLE

Impact of insulin pumps on glycaemic control in a pump-naïve paediatric regional population

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Aim: To examine the clinical impact of insulin-pump therapy for children with type 1 diabetes mellitus (T1DM) in a regional paediatric service, Auckland, New Zealand.

Methods: Retrospective analysis of children with T1DM from the Starship paediatric diabetes database who started on insulin-pump therapy from 2002 to 2008 compared with the whole T1DM population and with an equal number of non-pump patients matched by age, sex, ethnicity and duration of diabetes.

Results: From 621 subjects with 6680 clinic visits, 75 children were treated with insulin-pump therapy for more than 12 months. Transitioning to insulin-pump treatment was associated with an improvement in HbA1c compared with baseline (−0.3%/year, $P < 0.001$) for up to 3 years. In contrast, despite similar deprivation scores, non-pump controls showed a continuing trend to higher HbA1c values (+0.2%/year, $P < 0.01$). The risk of severe hypoglycaemia fell after pump start (from 27 (0–223) to 5 (0–0.91) events/100 patient years) with no change in non-pump controls; the rate of diabetic ketoacidosis remained low in both groups.

Conclusions: In a pump-naïve regional paediatric population, insulin-pump therapy for T1DM was safe and effective, and associated with sustained improvements in HbA1c and lower risk of hypoglycaemia.

Key words: adolescent; endocrinology.

What is already known on this topic

- 1 Continuous subcutaneous insulin infusion using insulin pumps is associated with a modest improvement in glycaemic control in randomised controlled trials.
- 2 Hypoglycaemia may be reduced with insulin-pump therapy, but this may not be achieved in children.

What this paper adds

- 1 With appropriate clinical support insulin-pump therapy can be successfully translated into clinical practice.
- 2 Patients starting on insulin pumps in routine practice had better glycaemic control before starting on pump treatment than matched controls who did not.
- 3 The improvement in glycaemic control and reduction in risk of hypoglycaemia were sustained for at least 3 years.

Continuous infusion of rapid-acting insulin by insulin pumps is increasingly popular in children with type 1 diabetes mellitus (T1DM). This popularity has been driven primarily by patient and parent choice rather than compelling evidence of clinical benefit.¹ Despite an increasing number of reports of insulin-pump therapy in children, the recent Cochrane review identified just seven high quality randomised trials in children and

adolescents, involving relatively few participants and most reporting relatively ~~short~~-short-term (6–12 months) follow-up.^{1–8} In this small dataset, pump treatment was associated with a significant improvement in HbA1c (−0.2%), along with a net reduction in insulin requirements. Data on severe hypoglycaemia were not suitable for meta-analysis. Although some retrospective reviews and non-randomised studies suggest a reduction in severe hypoglycaemic events,^{7,9} others suggest no significant effect on hypoglycaemia in children.¹⁰ The current NICE guidelines recommend insulin-pump therapy as a treatment option within the framework of a trained specialist team.¹¹

It is unclear how well these apparent clinical benefits seen in randomised clinical trials translate into clinical practice. This is a major concern, as quality of control of T1DM may be affected by many variables including the pervading financial climate,

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1 patient selection and motivation, and the insulin-pump experi-
2 ence of the medical team.

3 New Zealand is an example of a social security system that
4 provides medical care free of charge, but with very limited
5 public and/or private funding for insulin-pump therapy
6 for children. The only retrospective audit of pump use in
7 New Zealand to date included no younger children with
8 T1DM, and just 27 adolescents. They reported a mean reduc-
9 tion in HbA1c from 9.1 to 8.1% after 3 months of pump
10 usage, with no pre-pump or long-term follow-up analysis or
11 comparison group.¹² Duration of follow-up is critical as chil-
12 dren with T1DM show a strong trend to worse control with
13 greater duration of diabetes.¹³ Interestingly, some studies in
14 adults have reported significant reductions in HbA1C during
15 the initial run-in period, which may reflect increased educa-
16 tion and blood glucose monitoring during the lead up to
17 insulin pump start.¹⁴

18 The aim of this study was to assess the impact of insulin-
19 pump use in the Auckland region on glycaemic control com-
20 pared with baseline values and with non-pump matched
21 controls with similar age, sex, ethnicity and duration of
22 diabetes.

23 **Methods**

24 **All subjects**

25 Children or adolescents with T1DM who attended for regular
26 follow-up clinics with the Auckland Paediatric Diabetes service
27 between 1 January 2002 and 31 December 2008 were included
28 in this study. All signed consent for their de-identified informa-
29 tion are stored at diagnosis and in follow-up. All subjects were
30 assessed 3 monthly, and clinical and demographic data includ-
31 ing HbA1c, self-reported frequency of blood glucose self-
32 monitoring, total daily dose of insulin, number of insulin
33 injections per day, episodes of hypoglycaemia and diabetic
34 ketoacidosis (DKA), and body mass index (BMI) were recorded.
35 BMI z-scores were calculated in accordance to the 2000 Centers
36 for Disease Control growth data.¹⁵

37 HbA1c was measured using a DCA 2000 Analyzer. This is
38 validated on a weekly basis to the hospital laboratory HPLC,
39 analyser as well as each machine being standardised to the HFCG
40 manufacturer standard (Siemens, USA).¹²

41 Episodes of moderate-severe hypoglycaemia were defined as
42 decreased level of consciousness and/or seizure, requiring assis-
43 tance from others including the use of glucagon rescue or
44 requiring ambulance assistance/hospital admission. Self-
45 reporting of severe hypoglycaemia was also cross referenced to
46 admissions to Starship Children's Hospital with hypoglycaemia
47 as a primary diagnosis.

48 DKA was defined as an admission to hospital with a recorded
49 pH by venous blood gas of <7.25, with ketonuria or ketonemia;
50 DKA at initial diagnosis was excluded. Ethnicity was defined by
51 self-report using a prioritised system, such that if multiple eth-
52 nicities were selected, the patient was assigned to a single cat-
53 egory, following a hierarchical classification of Maori, Pacific,
54 other and then European.

55 Approval for this study was given by the Northern Y Regional
56 Ethics Committee.

57 **Pump group**

58 Eligible patients had a minimum of 12 months continuous use
59 of an insulin pump, irrespective of metabolic control and regular
60 clinic attendance before and after pump start. All patients had to
61 register with the pump program and show that they could
62 perform multiple blood tests and records a day, were regular
63 clinic attendees and had up-to-date knowledge of carbohydrates
64 and desired to go on a pump. Each pump start was tailored to
65 the age and stage of the child's and family's capabilities, and
66 24/7 back-up and advice were available; the same level of
67 support was also provided to all children with T1DM. Approxi-
68 mately 50% of insulin pumps were donated from charity and
69 were prioritised to children with recurrent hypoglycaemia,
70 coeliac disease or early complications such as persistent micro-
71 albuminuria. The remaining ~50% of pumps were self-
72 purchased or self-funded. All patients received the same
73 level of support, training and back-up for pump start and in
74 follow-up. There is no funding for consumables in New Zealand.

75 **Non-pump matched controls**

76 Non-pump controls were matched to pump patients by age,
77 time from diagnosis, ethnicity and gender using propensity
78 score analysis, and then individual (one-to-one) matches
79 chosen based on data availability across similar durations. The
80 duration of diabetes at pump initiation for each pump patient
81 was used to determine a 'matched start time' for each matched
82 control and to compile standardised time-point data as
83 described later. Because of inherent differences in the duration
84 of diabetes, duration of pump therapy and completeness of
85 clinical data, not all time points include 100% of subjects.
86 Excluding time points with <15 control or pump patients
87 allowed analysis for the period from 24 months before to
88 36 months after pump initiation.

89 **Socio-economic status**

90 SES was classified using the New Zealand Index of Deprivation
91 2001. This used household census data reflecting nine aspects of
92 material and social deprivation to divide New Zealand into
93 tenths (scored 1–10) by residential address, with 1 being the
94 least deprived. Scores are derived from small area units each
95 reflecting approximately 90 people.¹⁶

96 **Data analysis**

97 All clinic data were 'standardised' based on pump-start or
98 matched start time as time-point zero. For analysis, clinic data
99 were then standardised to 6- to 12-monthly time points. HbA1c
100 data were calculated as the average of the patient's data col-
101 lected within 3 months either side of that time. BMI and insulin
102 dose are for the clinic closest to that time point. Analysis was
103 undertaken using JMP 8.0 (SAS Inc., Cary, NC, USA). Time-
104 point comparisons were undertaken by *t*-test (for single time-
105 point comparison) or analysis of variance (for comparison of
106 rates of change).¹⁴ ¹⁵ ¹⁶

Table 1 Demographic data for all non-pump- and pump-group children with T1DM in the Auckland region, New Zealand, 2002–2008.

	Non-pump (n = 546)	Pump (n = 75)	Significance
Age at diagnosis (years)	7.8 ± 3.9	6.0 ± 3.6	<0.0001
Ethnicity (% European)	68	92	0.0002
Gender (% female)	47	53	0.32
Clinic visits (whole study period)	10.1 ± 7.2	15.8 ± 5.5	<0.0001
Deprivation index	5.1 ± 2.9	4.4 ± 2.8	0.05

T1DM, type 1 diabetes mellitus.

Table 2 Demographic data for matched controls and the pump group.

	Controls (n = 75)	Pump (n = 75)	Significance
Age at diagnosis (years)	6.1 ± 3.6	6.0 ± 3.6	0.88
Ethnicity (% European)	92%	92%	1.00
Gender (% female)	53%	53%	1.00
Deprivation index	4.5 ± 2.8	4.4 ± 2.8	0.73
Clinic visits (whole study period)	16.7 ± 6.0	15.8 ± 5.5	0.34
HbA1c at pump start* (matched pump start – matched for time since diagnosis)	8.4 ± 1.1*	8.1 ± 0.8	0.03

**ns*.

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Results

All subjects

For the study period there were 621 patients with T1DM with 6680 visits; their demographic data are shown in Table 1. Seventy-eight insulin-pump starts were identified, of whom three discontinued pump therapy before 12 months and were excluded, leaving 75 pump patients (Tables 1 and 2). Further two subjects who discontinued pump therapy after 12 months were included in the analysis. There were 31 pump patients at 24 months and 20 patients at 36 months. During the first 24 months, there was no difference in metabolic control between pump patients with <2 or >2 years of follow-up. The non-pump matched-control group was selected from the 546 pump-naïve subjects remaining (n = 75, Table 2).

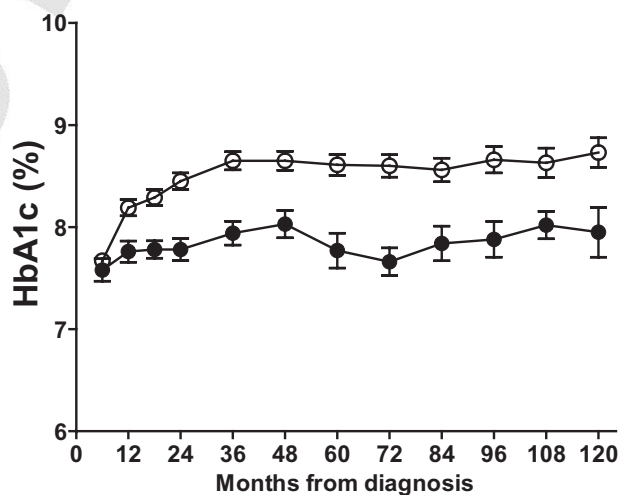


Fig. 1 Time sequence of changes in HbA1c after diagnosis in all non-pump subjects with T1DM in the Auckland region (n = 546, open circles) and patients who started on insulin-pump treatment for at least 12 months (n = 75, closed circles). Time zero represents T1DM diagnosis. The average age of pump start from diagnosis was 4.3 years. Data are mean ± SEM. SEM, standard error of the mean; T1DM, type 1 diabetes mellitus.

Insulin-pump versus all non-pump patients

Compared with all non-pump patients with T1DM, patients who transferred to an insulin pump were younger at diagnosis, were less deprived, attended clinic more frequently, were predominantly European and had better glycaemic control (Table 1). The non-pump patients showed a greater secular trend than pump patients to increasing HbA1c over time (Fig. 1, $P < 0.001$). Glycaemic control was significantly better in pump patients from 12 months after diagnosis of T1DM, well before starting insulin-pump therapy ($P < 0.001$) (on average insulin-pump treatment was initiated 4.3 years after diagnosis).

Effect of insulin-pump start

Changes in HbA1c, insulin dose and BMI before and after pump start are shown for the insulin pump and matched controls in

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Figure 2. The insulin-pump group shows increasing HbA1c over time before pump start ($P = 0.03$) and then a sustained fall in HbA1c of -0.3% per year after pump start ($P < 0.001$). Consistent with this, insulin doses increased progressively before pump start ($+0.06$ U/kg/day/year, $P = 0.03$), followed by a fall in insulin doses of -0.09 units/kg/year after pump start ($P < 0.05$). There was no significant effect of pump start on BMI standard deviation score (SDS) (BMI SDS changed 0.01 per year before pump to -0.11 after insulin pump, $P = 0.14$).

Insulin pump versus matched controls

Glycaemic control differed overall between those who were to go on pumps and the non-pump controls: $+0.60\%$ for period 12–24 months before pump; $P = 0.002$. There was a continuing increase in HbA1c in matched controls after pump start, and it remained higher than the pump group throughout the follow-up period ($P < 0.01$). After 36 months, although there was an apparent trend for HbA1c to rise in pump group, this was not significant, and HbA1c levels remained better than in matched controls.

As shown in Figure 2b, there was no difference in insulin dose prior to pump start, but a significantly difference then persisted, with less insulin requirement in the pump group ($P < 0.05$). There was no significant change in BMI SDS in either group throughout the study period (see Figure 2c).

Severe hypoglycaemia

The rates of hypoglycaemia were not different between groups before pump start (27 vs. 22 events/100 patient years, pump vs. non-pump patients, respectively, $P = 0.4$). In contrast, there was a sustained reduction after pump start in the pump but not the non-pump group (5 vs. 22/100 patient years, $P < 0.001$).

DKA

There was no significant difference in the rate of DKA before (0.01 events/year vs. 0.07 events/year, pump vs. non-pump, $P = 0.06$) or after pump start (0.07 events/year in both groups, $P =$ non-significant).

Discussion

The present study demonstrates that in a regional population of children with T1DM supported by a dedicated clinical team, routine clinical use of insulin-pump therapy was associated with a significant improvement in glycaemic control, reduced total insulin requirement and markedly reduced risk of severe hypoglycaemia compared with baseline and matched controls. The reduction in HbA1c was maintained for up to 3 years after pump start.

The apparent benefits of pump treatment in the present study are consistent with meta-analysis findings,¹¹ likely in part related to selection of motivated families and strong team support, as discussed next. Critically, the improvement in HbA1c levels among pump patients was associated with reduced, not increased, risk of hypoglycaemia,¹⁷ further alleviating historic concerns about severe hypoglycaemia seen with

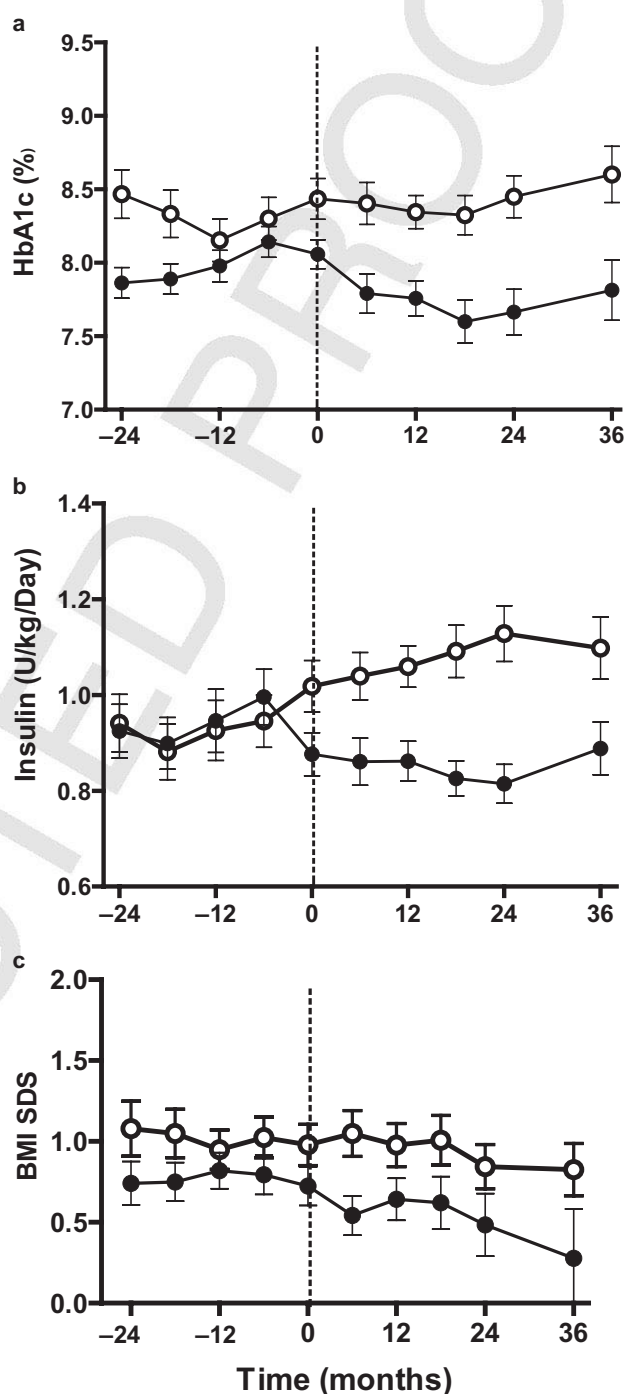


Fig. 2 HbA1c (%), insulin dose (U/kg/day) and BMI SDS in the pump group ($n = 75$, solid circles) and matched non-pump controls ($n = 75$, open circles) before and after pump start (time zero). The dotted vertical line represents pump start or 'matched-pump start'. Data are mean \pm SEM. BMI, body mass index; SEM, standard error of the mean; SDS, standard deviation score.

1 outdated insulin-pump technology.^{2,17} Hypoglycaemic seizures
2 are a major concern for patients and parents and, in the long
3 term, are associated with a small but cumulative loss of intelli-
4 **19** gence quotient.¹⁸ The present study also supports previous
5 reports that there was no increase in BMI during insulin-pump
6 treatment.^{19,20} The rate of DKA was similar in both groups, but
7 this study was not powered to detect changes in this relatively
8 infrequent event.²¹ Although the impact of pump therapy on
9 quality of life was not assessed, the low total drop-out rate from
10 the pump program of 5/78 in the present study is consistent
11 with reported discontinuation rates in settings with markedly
12 better financial support.^{21,22}

13 This study is one of few studies of routine clinical pump use
14 that has compared outcomes with a matched-control group.
15 However, it is critical to appreciate the major potential limita-
16 tion of this study, that the groups were not randomised. Thus,
17 we cannot conclude that all children with T1DM would neces-
18 sarily benefit to the same extent from pump therapy. In the
19 Auckland region selection for insulin-pump therapy was and is
20 based on an approximately equal mixture of children with
21 recurrent severe hypoglycaemia, coexistent coeliac disease or
22 early complications, and patient and family choice. Reassur-
23 ingly, despite only being initially matched for age, sex and
24 duration of diabetes, there was no difference between groups
25 in HbA1c in 12 months prior to pump start nor of major deter-
26 minants of metabolic control including BMI, social deprivation
27 scores, ethnicity or insulin dose.¹³

28 Those patients who went on to pump therapy had
29 persistently lower HbA1c levels before initiation of pump
30 therapy compared with matched controls. This suggests that
31 they may be a more highly motivated subset of patients, inde-
32 pendent of socio-economic and ethnic differences. Socio-
33 economic status has been shown to predict poor glycaemic
34 control.¹³

35 There remain significant barriers to wider uptake of insulin-
36 pump technology in New Zealand, including the associated
37 cost,⁹ and the challenge of providing access to dedicated
38 support in multiple, relatively small regional centres. There is
39 minimal government or private insurance funding of insulin
40 pumps, in comparison with our close neighbour, Australia,
41 where there has been a marked uptake of insulin pumps by
42 children and adolescents supported by funding from govern-
43 ment, the Juvenile Diabetes Research Foundation and insur-
44 ance companies. Although insulin-pump treatment is clearly
45 not suitable for or even desired by all patients with T1DM, the
46 present study suggests that with appropriate team support,
47 pump treatment can significantly improve glycaemic control in
48 routine clinical practice, and thus wider access is likely to be
49 **20** beneficial.²³

51 Conclusions

52 In our pump-naïve regional paediatric population insulin-pump
53 therapy was safe and effective, associated with sustained
54 improvements in HbA1c. There was a dramatic improvement in
55 the incidence of severe hypoglycaemia. It is hoped that these
56 benefits can be translated to a wider groups of pump users as
57 funding improves.

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21 58

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59 tion's ongoing support, the donation of insulin pumps and
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61 acknowledge for additional provision of insulin pumps directly
62 to families. 63 64

References

- 65 1 Cohen D, Weintrob N, Benzaquen H, Galatzer A, Fayman G, Phillip M. Continuous subcutaneous insulin infusion versus multiple daily injections in adolescents with type I diabetes mellitus: a randomized open crossover trial. *J. Pediatr. Endocrinol. Metab.* 2003; **16**: 1047–50. 66 67
- 2 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 Syst. Rev.* 2010; (1): CD005103. 68 69 70 71 72 73 74
- 3 Doyle EA, Weinzimer SA, Steffen AT, Ahern JA, Vincent M, Tamborlane WV. A randomized, prospective trial comparing the efficacy of continuous subcutaneous insulin infusion with multiple daily injections using insulin glargine. *Diabetes Care* 2004; **27**: 1554–8. 75 76 77 78
- 4 Meschi F, Beccaria L, Vanini R, Szulc M, Chiumello G. Short-term subcutaneous insulin infusion in diabetic children. Comparison with three daily insulin injections. *Acta Diabetol. Lat.* 1982; **19**: 371–5. 79 80 81
- 5 Nuboer R, Borsboom GJ, Zoethout JA, Koot HM, Bruining J. Effects of insulin pump vs. injection treatment on quality of life and impact of disease in children with type 1 diabetes mellitus in a randomized, prospective comparison. *Pediatr. Diabetes* 2008; **9**: 291–6. 82 83 84 85
- 6 Pozzilli P, Crino A, Schiaffini R et al. A 2-year pilot trial of continuous subcutaneous insulin infusion versus intensive insulin therapy in patients with newly diagnosed type 1 diabetes (IMDIAB 8). *Diabetes Technol. Ther.* 2003; **5**: 965–74. 86 87 88 89
- 7 Skogsberg L, Fors H, Hanas R, Chaplin JE, Lindman E, Skogsberg J. Improved treatment satisfaction but no difference in metabolic control when using continuous subcutaneous insulin infusion vs. multiple daily injections in children at onset of type 1 diabetes mellitus. *Pediatr. Diabetes* 2008; **9**: 472–9. 90 91 92 93 94
- 8 Weintrob N, Schechter A, Benzaquen H et al. Glycemic patterns detected by continuous subcutaneous glucose sensing in children and adolescents with type 1 diabetes mellitus treated by multiple daily injections vs continuous subcutaneous insulin infusion. *Arch. Pediatr. Adolesc. Med.* 2004; **158**: 677–84. 95 96 97 98 99
- 9 Danne T, Tamborlane W. Insulin pumps in pediatrics: we have the technology. We have the evidence. Why are still so few kids using it? *Pediatr. Diabetes* 2006; **7**: 2–3. 100 101 102
- 10 Pankowska E, Blazik M, Dziechciarz P, Szypowska A, Szajewska H. Continuous subcutaneous insulin infusion vs. multiple daily injections in children with type 1 diabetes: a systematic review and meta-analysis of randomized control trials. *Pediatr. Diabetes* 2009; **10**: 52–8. 103 104 105 106 107
- 11 NICE. Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus; 2008. 108 109
- 12 Reda E, Von Reitzenstein A, Dunn P. Metabolic control with insulin pump therapy: the Waikato experience. *N. Z. Med. J.* 2007; **120**: U2401. 110 111 112
- 13 Carter PJ, Cutfield WS, Hofman PL et al. Ethnicity and social deprivation independently influence metabolic control in children with type 1 diabetes. *Diabetologia* 2008; **51**: 1835–42. 113 114 115
- 14 Hoogma R, Hoekstra J, Michels B, Levi M. Comparison between multiple daily insulin injection therapy (MDI) and continuous subcutaneous insulin infusion therapy (CSII), results of the five nations study. *Diabetes Res. Clin. Pract.* 2006; **74**: S144–7. 116 117 118 119

- 1 15 **Centers-for-Disease-Control-and-Prevention**. A SAS program for the 16
2 CDC growth charts. 2009. 17
- 3 16 Salmond C, Crampton P. NZDep2001 index of deprivation user's 18
4 manual. In: Department of Public Health, Wellington School of 19
5 Medicine and Health Sciences; 2002. 20
- 6 17 Lenhard MJ, Reeves GD. Continuous subcutaneous insulin infusion: a 21
7 comprehensive review of insulin pump therapy. *Arch. Intern. Med.* 22
8 2001; **161**: 2293–300. 23
- 9 18 **DCCT-Research-Group** Effect of intensive diabetes treatment on the 24
10 development and progression of long-term complications in 25
11 adolescents with insulin-dependent diabetes mellitus: diabetes 26
12 control and complications trial. Diabetes Control and Complications 27
13 Trial Research Group. *J. Pediatr.* 1994; **125**: 177–88. 28
- 14 19 Maniatis AK, Klingensmith GJ, Slover RH, Mowry CJ, Chase HP. 29
15 Continuous subcutaneous insulin infusion therapy for children and
adolescents: an option for routine diabetes care. *Pediatrics* 2001; **107**: 351–6. 16
- 20 Ahern JA, Boland EA, Doane R *et al.* Insulin pump therapy in 17
pediatrics: a therapeutic alternative to safely lower HbA1c levels 18
across all age groups. *Pediatr. Diabetes* 2002; **3**: 10–15. 19
- 21 Hanas R, Ludvigsson J. Hypoglycemia and ketoacidosis with insulin 20
pump therapy in children and adolescents. *Pediatr. Diabetes* 2006; **7** 21
(Suppl. 4): 32–8. 22
- 22 Hofer SE, Heidtmann B, Raile K *et al.* Discontinuation of insulin pump 23
treatment in children, adolescents, and young adults. A multicenter 24
analysis based on the DPV database in Germany and Austria. *Pediatr.* 25
Diabetes 2009; **11**: 116–21. 26
- ~~23 Statistics New Zealand. Subnational population estimates: at 30 June 27
2009. In: Wellington; 2010. 28~~

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