

Original article

Glycemic control and weight outcomes after initiation of continuous subcutaneous insulin infusion therapy[☆]



C. Esteves^{a,b,*}, S. Belo^{a,b}, M.C. Neves^{a,b}, C. Arteiro^a, D. Carvalho^{a,b}

^a Endocrinology, Diabetes and Metabolism Department, Centro Hospitalar São João, Porto, Portugal

^b Faculty of Medicine, University of Porto, Porto, Portugal

ARTICLE INFO

Article history:

Received 23 April 2014

Accepted 10 February 2015

Available online 15 June 2015

Keywords:

Insulin infusion system

Type 1 diabetes mellitus

Gender

ABSTRACT

Introduction: The continuous subcutaneous insulin infusion (CSII) is an alternative to multiple daily injections therapy in type 1 diabetes and its use is increasingly common due to the beneficial effects on glucose control.

Aims: To analyze clinical features and biochemical parameters of patients on CSII therapy.

Type of study: Longitudinal retrospective.

Setting: Outpatient clinic.

Population: Type 1 diabetic patients using insulin infusion pump in our department.

Methods: We evaluated outcomes regarding the following set points: immediately before initiation of CSII therapy, 12 months after inclusion and in the last appointment. For statistical analysis, we used non-parametric tests and linear regression analysis. We considered significant a value of $p \leq 0.05$.

Results: We studied 63 patients (24 men; 39 women) with a mean pre-CSII HbA1c of $8.2\% \pm 1.43$; mean age at the time of placement of 32.7 ± 10.94 years; and mean follow up time after placement of 2.1 ± 1.92 years. There was a statistically significant reduction of HbA1c during follow-up (HbA1c 12 months: $7.2\% [6.6-7.8]$ $p = 0.001$; HbA1c at the end of follow-up: $7.4\% [6.6-7.9]$ $p = 0.001$). There was no significant variation of weight or total daily insulin dose. We registered a negative correlation between the last HbA1c before CSII and the reduction in HbA1c until the end of the follow-up period ($\rho = -0.644$ $p = 0.000$). The median reduction in HbA1c was higher in women (W: $-1.10 [-2.20--0.40]$ vs M: $-0.10 [-0.80-0.40]$; $p = 0.002$). Female gender was a predictive factor of better results with CSII, even after adjustment to the last HbA1c before the initiation of therapy.

Conclusions: In our sample, the last HbA1c before the beginning of CSII was the most powerful predictive factor of the reduction of HbA1c during follow up. Women had better results than men. There was no significant variation of weight and total daily insulin dose during follow up.

© 2014 Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Evolução do controle metabólico e do peso após início de terapêutica de infusão subcutânea contínua de insulina

RESUMO

Introdução: A terapêutica com infusão subcutânea contínua de insulina (Tisi) é uma opção ao uso de múltiplas injeções de insulina na diabetes tipo 1 e o seu uso é cada vez mais frequente dados os benefícios no controle glicémico.

Objetivos: Analisar as características clínicas e os parâmetros bioquímicos dos doentes tratados com Tisi e procurar fatores preditores da resposta à terapêutica.

Tipo de estudo: Longitudinal retrospectivo.

Local: Consulta externa.

População: Diabéticos tipo 1 usuários de Tisi seguidos no nosso serviço.

Palavras chave:

Bomba de infusão subcutânea de insulina

Diabetes mellitus tipo 1

Gênero

[☆] Presented at the ICE/ECE 2012 meeting with a grant provided by the Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo.

* Corresponding author.

E-mail address: cme1983@gmail.com (C. Esteves).

Métodos: Foram registrados os resultados nos seguintes períodos: imediatamente antes da colocação da Tisi, 12 meses após colocação e à data da última consulta. Os resultados foram apresentados como média \pm desvio padrão ou mediana [quartis]. Foram usados testes não paramétricos para a análise estatística e foi efetuada regressão linear. Foram considerados significativos os valores de $p < 0,05$.

Resultados: A amostra era constituída por 63 diabéticos tipo 1 (24 homens - H; 39 mulheres - M) com os seguintes valores antes da colocação: idade $32,7 \pm 10,94$ anos; HbA1c $8,2\% \pm 1,43$. O tempo médio de catamnese foi de $2,1 \pm 1,92$ anos. Ocorreu uma redução estatisticamente significativa da HbA1c ao longo do tempo de seguimento (HbA1c aos 12 meses: $7,2\%$ [6,6-8] $p = 0,001$; HbA1c ao fim do tempo de seguimento: $7,4\%$ [6,6,7,9] $p = 0,001$). Não se verificou variação do peso e da dose diária total de insulina. Verificou-se uma correlação negativa entre a HbA1c prévia e a redução da HbA1c até ao fim do tempo de seguimento ($\rho = -0,644$ $p = 0,000$). A mediana da redução da HbA1c até a data da última consulta foi maior no grupo das mulheres (M: $-1,10$ [$-2,20$ - $-0,40$] vs. H: $-0,10$ [$-0,80$ - $-0,40$]; $p = 0,002$). O género feminino foi um fator preditivo de melhor resposta à Tisi mesmo após ajuste para a HbA1c prévia.

Conclusões: Na amostra estudada, a última HbA1c anterior ao início da Tisi foi o fator com maior capacidade de predição da resposta à terapêutica. As mulheres obtiveram melhores resultados da terapêutica com Tisi do que os homens. Não ocorreram variações estatisticamente significativas do peso ou da dose diária total de insulina.

© 2014 Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo. Publicado por Elsevier España, S.L.U. Este é um artigo Open Access sob a licença de CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

After the publication of the DCCT¹, the goal of the treatment of type 1 diabetes mellitus is to obtain glucose values as near as possible to normal, as long as the patient's hypoglycaemia risk isn't unacceptably high. The optimum glucose control would prevent the occurrence of chronic complications of diabetes² and result in improvement of the quality of life of the person with diabetes³. The review of target glucose values in type 1 diabetes mellitus has led to the increased use of intensive insulin therapy that was suggested by the same study as the most effective method to obtain the proposed goals.

Continuous subcutaneous insulin infusion (CSII) therapy is an alternative to the use of multiple daily injections (MDI) for the treatment of type 1 diabetes mellitus and its use is increasingly common due to the beneficial effects on glucose control. Pickup⁴ used CSII as a research tool to elucidate the relation between glucose control and diabetic complications. Later on, other authors described the improvement of glucose control in selected and motivated patients that previously had not attained the treatment goals with MDI.^{5–11} Although several studies showed significant reductions in HbA1c with CSII, a meta-analysis of randomized clinical trials comparing with MDI showed, by a random effects model, a non-significant trend towards mean reductions in HbA1c of $-0,26$ (IC 95% $-0,57$ – $0,05$) after 6 months follow up and $-0,61$ (IC 95% $-1,29$ – $0,07$) after 12 months follow up⁷. Other authors¹² detected significant reductions in HbA1c ($9,36 \pm 0,22$ vs $8,96 \pm 0,11$, $p = 0,039$). Significant differences between therapeutic modalities are only apparent with follow up periods longer than 1 year.

Regarding hypoglycaemia risk, several observational studies suggest that CSII is associated with a significant risk reduction, particularly in terms of severe episodes⁷. The same meta-analysis did not find data supporting sustained reductions in total daily insulin dose (TDID) in patients using CSII, nor significant reductions in weight. Other authors^{12,13} suggest that CSII might be associated with as much as 16% reductions in TDID comparing with multiple daily injections, as well as a significant increase in weight ($68,2 \pm 0,7$ Kg vs $71,2 \pm 0,3$ Kg; $p < 0,001$).

Greater patient satisfaction has been documented in patients using CSII therapy, although there is discordance between studies in terms of impact on quality of life^{3,6,7,14}. However, it is of note that CSII therapy might be associated with other complications, namely an increase in risk of diabetic ketoacidosis, pump malfunction and infusion site infections¹². Few studies have analyzed the variables associated with improved metabolic control after initiation of CSII

therapy. Two studies have shown greater benefit in individuals with higher HbA1c before CSII^{15,16}. The selection of patients with higher HbA1c (HbA1c $> 8,0\%$) was associated with superior benefit than described in two meta-analysis^{12,13}.

There is no significant data regarding the effect of age in CSII but several authors have suggested good results in pediatric patients in terms of HbA1c reduction as well as in risk of hypoglycaemia and quality of life¹⁷. One study on female adolescents showed a good response to CSII therapy in this population, which included individuals with eating disorders¹⁸.

Aims

To analyze the clinical characteristics and biochemical parameters in diabetic patients treated with CSII therapy and identify the predictive factors for a good response to this regimen.

Methods

We included all individuals with type 1 diabetes that were users of CSII, under follow up in the Endocrinology consultation of our hospital. We recorded variables in the following time points: immediately before initiation of CSII therapy, 12 months after initiating use of the insulin pump and at the time of the last appointment. As the TDID is not recorded in the patient's clinical file, it was inferred from the insulin sensitivity factor, which is calculated using the 1800 rule, universally used in our consultation. Results were presented as mean \pm standard deviation or median [quartiles]. Changes in weight, TDID and TDID/Weight ratio were calculated as fractions. For the statistical analysis, we used SPSS Statistics 20.0. To compare differences in the variables and their correlations we used the Wilcoxon test, Mann-Whitney test, Spearman correlation and a linear regression model. We considered significant a value of $p \leq 0,05$. In a separate analysis, the sample was divided in two groups (better and worse response) according to the median of variation in HbA1c at the end of follow up ($-0,8\%$), and we used the Mann-Whitney and Fischer exact tests to compare groups.

Results

The sample included 63 patients with type 1 diabetes (24 men; 39 women) whose clinical characteristics are presented in Table 1. The mean follow up was $2,08 \pm 1,920$ years.

Table 1
Characterization of the sample (n 63: 24♂ 39♀).

Age at diagnosis (years)	17.25 ± 10.811
Age at the time of initiation of CSII (years)	32.70 ± 10.942
Age (years)	35.63 ± 11.467
Duration of diabetes (years) at the time of initiation of CSII	17.98 ± 9.006
Duration of follow up (years)	2.08 ± 1.920
Pre-CSII HbA1c (%)	8.167 ± 1.4277
HbA1c 12 months (%)	7.391 ± 1.1145
HbA1c at the end of follow up (%)	7.507 ± 1.2350
Pre-CSII weight (Kg)	72.27 ± 11.891
Weight 12 months (Kg)	67.52 ± 10.986
Weight at the end of follow up (Kg)	70.89 ± 14.678
Pre-CSII TDID (UI)	52.0168 ± 14.80194
TDID/Weight (UI/Kg)	0.73 ± 0.189
TDID 12 months (UI)	47.0371 ± 13.09964
TDID/Weight (UI/Kg)	0.66 ± 0.146
TDID at the end of follow up (UI)	48.8544 ± 19.10247
TDID/Weight (UI/Kg)	0.68 ± 0.185

TDID–total daily insulin dose

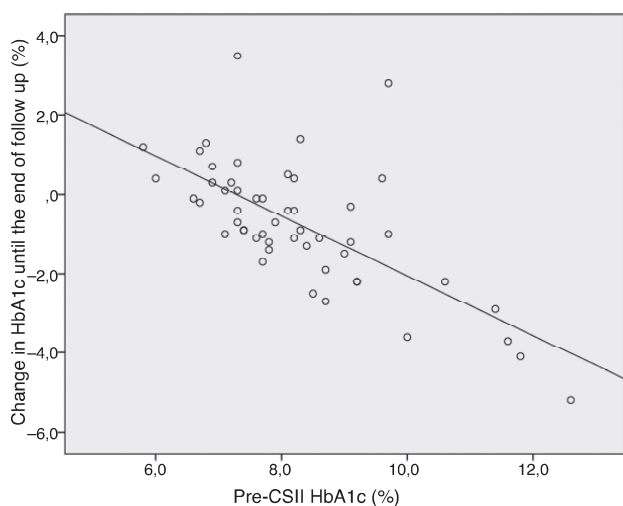


Figure 1. Scatter plot–pre-CSII HbA1c–Variation of HbA1c at the end of follow up.

General outcomes. After CSII initiation, there was a significant mean HbA1c reduction at 12 months and at the end of the follow up period (Table 2). There was no significant variation in weight, TDID or TDID/weight ratio.

HbA1c. We found a significant correlation between pre-CSII HbA1c and its variation at 12 months and at the end of follow up ($\rho = -0.643$ $p = 0.000$ and $\rho = -0.644$ $p = 0.000$, respectively)–figure 1. The linear regression model showed that for each 1.0% increase in pre-CSII HbA1c there is a 0.76% reduction in post-CSII HbA1c ($R = 0.682$, $t = -6.593$, $p = 0.000$). We found a significant correlation between HbA1c variation at 12 months and age at the time of initiation of CSII therapy ($\rho = 0.312$ $p = 0.033$) and between HbA1c variation at the end of follow up and age at diagnosis ($\rho = 0.390$ $p = 0.005$) and pre-CSII TDID ($\rho = -0.402$ $p = 0.025$). The total time of follow up had a significant correlation with pre-CSII HbA1c ($\rho = 0.260$ $p = 0.049$) and with the variation of HbA1c at 12 months

Table 2
Clinical and biochemical outcomes after initiation of CSII.

	Pre-CSII	12 months	End of follow up
HbA1c (%)	7.8 [7.23–8.78]	7.2 [6.60–7.80] $p = 0.001$	7.4 [6.60–7.90] $p = 0.001$
Weight (Kg)	72.0 [53–98]	65.0 [51–94] $p = 0.103$	67.0 [52–105] $p = 0.721$
TDID (UI)	50.0 [41.86–60.00]	45.0 [40.02–52.94] $p = 0.102$	45.0 [36.00–56.25] $p = 0.420$

Results of HbA1c and TDID are presented as median [1st quartile–3rd quartile] and weight is presented as median [minimum–maximum]. $p < 0.05$ was considered significant.

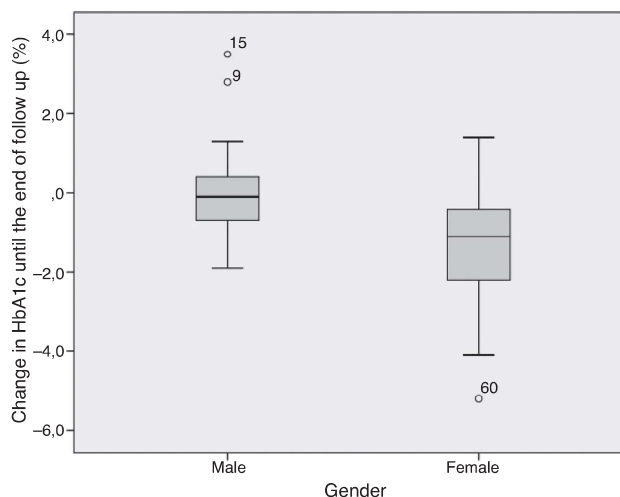


Figure 2. Box plot–Gender differences in HbA1c variation until the end of the follow up period.

and end of follow up ($\rho = -0.448$ $p = 0.002$ e $\rho = -0.304$ $p = 0.028$). The linear regression model showed that the total time of follow up is not a predictive factor of HbA1c variation at 12 months or at the end of follow up, after adjustment to the pre-CSII ($p = 0.403$ e $p = 0.106$, respectively).

Gender. In the comparative analysis, we found a significant difference in HbA1c variation until the end of follow up, with a more pronounced reduction in women comparing to men (median [quartile]: -1.100 [-2.200 – -0.400] vs -0.100 [-0.800 – 0.400]; $p = 0.002$)–figure 2. It is of note that the two groups were not significantly different in terms of pre-CSII HbA1c (Men: 7.7 [7.2 – 8.2] vs Women: 8.2 [7.3 – 9.2]; $p = 0.119$).

We evaluated the interaction between pre-CSII HbA1c and gender as determinants of variation of HbA1c until the end of the follow up period. According to this model, these two variables predict 52.3% of the variance of HbA1c. Female gender is associated with a 0.824 reduction in HbA1c ($t = -2.449$; $p = 0.018$) and each 1.0% increase of the pre-CSII HbA1c is associated with a 0.67% reduction in HbA1c ($t = -5.869$; $p = 0.000$)–Table 3.

Table 3
Univariate linear regression models for pre-CSII HbA1c and gender. Multivariate linear regression model including pre-CSII HbA1c and gender as independent covariates and a dependent variable - change in HbA1c until the end of the follow up period.

Univariate linear regression model				
	R ²	Regression coefficient	t	p
Pre-CSII HbA1c	0.465	-0.756	-6.593	0.000
Gender (female)	0.188	-1.413	-3.406	0.001
Multivariate linear regression model (R ² = 0.523)				
	Regression coefficient	t	p	
Gender	-0.824	-2.449	0.018	
Pre-CSII HbA1c	-0.672	-5.869	0.000	

Weight and TDID. We found a significant correlation between weight and TDID, and between the weight variation and TDID variation until the end of the follow up period ($\rho=0.557$ $p=0.031$). There is a significant correlation between pre-CSII TDID and its variations at 12 months and end of follow up ($\rho=-0.561$ $p=0.005$ and $\rho=-0.619$ $p=0.001$, respectively), as well as with pre-CSII HbA1c and HbA1c variation until the end of follow up ($\rho=0.381$ $p=0.024$ and $\rho=-0.402$ $p=0.025$, respectively). The pre-CSII TDID/weight ratio has a significant correlation with the variation in TDID/weight ratio until the end of follow up ($\rho=-0.771$ $p=0.001$).

Characterization of groups according to the quality of response. The sample was divided in two groups according to the median HbA1c variation until the end of follow up: a reduction in HbA1c > 0.8% was considered a «better response» (BR) and a reduction in HbA1c inferior or equal to 0.8%, a stable HbA1c or an increase in HbA1c were considered a «worse response» (WR). When the two groups were compared, we found a significant difference between pre-CSII HbA1c (BR 8.65% [7.775–9.775] vs WR 7.30% [6.900–8.100]; $p=0.000$), age at diagnosis (BR 10.0 years [5.5–18.0] vs WR 20.0 years [12.25–26.0]; $p=0.003$) and age at the time of CSII initiation (BR 28.5 years [22.75–34.25] vs WR 33.0 years [27.5–41.5]; $p=0.028$). We found a significantly higher number of women in the group with a BR to CSII ($p=0.017$). There were no other significant differences between groups.

Discussion

In concordance with previous literature, we found a significant reduction in HbA1c after initiation of CSII, representing a median variation in HbA1c of -0.50% [-1.20 – -0.1] at 12 months follow up and -0.80% [-1.475 – -0.3] at the end of follow up. These results suggest that there is a more marked reduction in HbA1c with longer periods of follow up, as reported by other authors¹². In our sample we did not find a significant change in weight, TDID or TDID/weight ratio.

The association between the improvement in glucose control with CSII and pre-CSII HbA1c was previously reported by Bode¹⁵ et al., as well as DeVries¹⁶. In concordance with those findings, we also report a negative correlation between pre-CSII HbA1c and its variation at 12 months and at the end of follow up.

Women had better outcomes with CSII than men, and this difference persisted even when adjusted to pre-CSII HbA1c. In a recent study¹⁹, this gender difference was reported, but the authors did not find a causal explanation for the results.

The fact that women presented with higher pre-CSII HbA1c values could be related to the existence of a patient subset with *brittle diabetes*²⁰. This classification is very controversial and little understood. The results of CSII therapy in *brittle diabetes* are very discordant between studies, some of which report benefit^{20–24}. However, it has already been reported improvement in metabolic control in female adolescents and young adults with CSII therapy¹⁸. Battaglia and colleagues considered that the studied population has a high prevalence of insulin injection omission, particularly in individuals with body image disorders, and showed that CSII was associated with a significant improvement in metabolic control, adherence to the prescribed regimen and better self-efficacy. Occasionally, this type of behavior is not identified, and these patients' diabetes is wrongly classified as *brittle*.

The response to the intervention in the group of women might also be related to other variables, which we did not evaluate, perhaps associated with the receptivity and adherence to new technologies, including the appropriate use of an insulin pump. It is also possible that there are other variables related to glucose control that we cannot infer from pre-CSII HbA1c.

The finding of a significant correlation between pre-CSII TDID and its variation at 12 months and at the end of follow up, and

with HbA1c variation can hypothetically be related to: 1) the individuals that most benefited from CSII therapy were already highly motivated and, beyond the rigorous compliance with their insulin regimen, they also increasingly adhered to their meal plan, with subsequent weight loss; 2) individuals that most benefited from CSII therapy were the ones that had more variability of their needs of insulin throughout the day and hence, were using a higher TDID under a MDI regimen; 3) individuals that most benefited from CSII therapy are the ones that tend to occasionally neglect insulin injections and are reported as keeping elevated HbA1c values despite using higher TDID.

The correlation between age at diagnosis and HbA1c variation at the end of follow up, and between age at the time of initiation of CSII and HbA1c variation at 12 months follow up can be related to the presence of a subset of older individuals in our sample, with the same duration of diabetes, and less capable of using electronic devices.

The characterization of two groups in terms of response to CSII confirmed our previous results, including the ones relative to a probable gender effect—higher prevalence of women in the BR group; the influence of pre-CSII HbA1c—individuals with higher HbA1c tend to obtain more benefit from CSII; age at diagnosis and at the time of initiation of the intervention—younger individuals have more marked reductions in HbA1c.

Limitations

Our study did not include other variables that might influence the success of CSII, such as patients' socioeconomic data (ie education level, employment pattern or characterization of the family aggregate), as this information was not originally included in our database. As ours is a convenience sample, we need to consider selection bias. On the other hand, we did not study the benefits of CSII in terms of incidence and severity of hypoglycaemia episodes and incidence of ketoacidosis. We considered information on hypoglycaemia unreliable because this was a retrospective study, and the registry is frequently based on subjective qualitative measures of incidence, as determined by several clinicians. On the other hand, ketoacidosis was extremely rare. We were also not able to extensively characterize the subgroup of women with greater improvement in metabolic control as our registry did not include more data on these patients, namely psychometric measures.

Conclusions

Women with type 1 diabetes mellitus seem to have greater benefit with CSII therapy, presumably in association with the existence of a subset of individuals with unsatisfactory glucose control with multiple daily injections. However, it is possible that other variables related with the female gender might contribute to this difference. Our findings should not interfere with priority criteria for the use of insulin pumps in type 1 diabetics.

References

1. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* 1993;329:977–86.
2. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Modern-Day Clinical Course of Type 1 Diabetes Mellitus After 30 Years' Duration. *Arch Intern Med.* 2009;169:1307–16.
3. Chantelau E, Schiffrers T, Schutze J, Hansen B. Effect of patient-selected intensive insulin therapy in quality of life. *Patient Educ Couns.* 1997;30:167–73.
4. Pickup JC, Keen H, Viberti GC, et al. Continuous Subcutaneous Insulin Infusion in the treatment of Diabetes Mellitus. *Diabetes Care.* 1980;3:290–300.
5. American Diabetes Association. Position Statement - Continuous Subcutaneous Insulin Infusion. *Diabetes Care.* 2004;27 Suppl 1:S110.

6. Cummins E, Royle P, Snaith A, Greene A, Robertson L, McIntyre L, et al. Clinical effectiveness and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes: systematic review and economic evaluation. *Health Technol Assess.* 2010;14:1–181.
7. 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;8:1–171.
8. Tamborlane WV, Shervin RS, Genel M, Felig P. Reduction to normal level of plasma glucose in juvenile diabetes by subcutaneous administration of insulin with a portable infusion pump. *N Engl J Med.* 1979;300:573–8.
9. Champion MC, Shepherd GAA, Rodger NW, Dupre J. Continuous subcutaneous infusion of insulin in the management of diabetes mellitus. *Diabetes.* 1980;29:206–12.
10. Schiffrin A, Belmonte ME. Comparison between continuous subcutaneous insulin infusion and multiple injections of insulin. *Diabetes.* 1982;31:255–64.
11. Home PD, Capaldo B, Burrin JM, Worth R, Alberti KGMM. A crossover comparison of continuous subcutaneous insulin infusion (CSII) against multiple insulin injections in insulin dependent diabetic subjects: improved control with CSII. *Diabetes Care.* 1982;5:466–71.
12. Pickup J, Mattock M, Kerry S. Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: meta-analysis of randomized controlled trials. *Br Med J.* 2002;324:705–10.
13. Weissberg-Benchell J, Antisdell-Lomaglio J, Seshadri R. Insulin pump therapy. A meta-analysis. *Diabetes Care.* 2003;26:1079–87.
14. Tsui E, Barnie A, Ross S, Parkes R, Zinman B. Intensive insulin therapy with insulin lispro: a randomized trial of continuous subcutaneous insulin infusion versus multiple daily insulin injection. *Diabetes Care.* 2001;24:1722–7.
15. Bode BW, Steed RD, Davidson PC. Reduction in severe hypoglycemia with long-term continuous subcutaneous insulin infusion in type 1 diabetes. *Diabetes Care.* 1996;19:324–7.
16. DeVries JH, et al. A randomized trial of continuous subcutaneous insulin infusion and intensive injection therapy in type 1 diabetes for patients with longstanding poor glycemic control. *Diabetes Care.* 2002;25:2074–6.
17. McMahon SK, Airey FL, Marangou DA, et al. Insulin pump therapy in children and adolescents: improvements in key parameters of diabetes management including quality of life. *Diabetic Medicine.* 2004;22:82–96.
18. Battaglia MR, Alemzadeh R, Katte H, Hall PL, Perlmutter C. Brief Report: Disordered Eating and Psychosocial Factors in Adolescent Females with Type 1 Diabetes Mellitus. *J Pediatr Psychol.* 2006;31:552–4.
19. Andersen HU, Hommel E, Andersen HC, et al: HbA1c and weight development one year after initiation of continuous subcutaneous insulin injection therapy in adult subjects. Poster #1102, 49th EASD Barcelona 2013. URL: <http://www.easdvirtualmeeting.org/resources/6204>
20. Voulgari C, Tentolouris N, Brittle Diabetes. A Contemporary Review of the Myth and Its Realization in Diabetes—Damages and Treatments. Prof. Everlon Rigobelo (Ed). InTech. 2011, 49–26.
21. Pickup J, Keen H. Continuous Subcutaneous Insulin Infusion at 25 years. *Diabetes Care.* 2002;25:593–5.
22. Pickup J, et al. Management of severely brittle diabetes by continuous subcutaneous and intramuscular insulin infusions: evidence for a defect in subcutaneous insulin absorption. *BMJ.* 1981;282, 347–3.
23. Petrovsky G, Dimitrovski C, Milenkovic T. Insulin pump therapy with continuous glucose monitoring improves metabolic control in brittle type 1 diabetes. *Prilozi.* 2007;28:129–35.
24. Kaufman F, et al. Insulin Pump Therapy in Type 1 Pediatric Patients: Now and Into the Year 2000. *Diabetes Metab Res Rev.* 1999;15:338–52.