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Review Article

Remission rates and predictors of continuous subcutaneous insulin infusions in type 2 diabetes: a systematic review and meta-analysis

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Abstract: Background: Continuous subcutaneous insulin infusions (CSII) can induce glycemic remission, a situation in which patients are able to maintain normoglycemia without anti-diabetic medications. The current systematic review and meta-analysis was conducted to assess remission rates of patients treated with CSII, aiming to identify predictors associated with remission outcomes. Methods: MEDLINE, Cochrane Library, and EMBASE databases were searched for clinical trials assessing remission rates of CSII in type 2 diabetes patients. Clinical characteristics of remission and non-remission groups were calculated as weighted mean differences (WMD) with associated 95% confidence intervals (CI). Remission rates were calculated by dividing the number of remission patients by the number of analyzed patients. Inverse variance statistical methods and fixed-effects analysis models were used to calculate pooled effects sizes, identifying possible remission predictors of CSII therapy. Results: Five studies, including 550 participants, were enrolled in the current study. Long-term drug-free remission rates of patients treated with CSII were 72.0% at 3 months of follow-up, 62.5% at 6 months, 50.4% at 12 months, and 37.1% at 24 months. Three trials compared clinical characteristics between remission and non-remission groups. Before CSII treatment, the remission group showed higher levels of BMI (WMD, 0.78), LnHOMA-IR (WMD, 0.17), and LnHOMA-B (WMD, 0.22). After treatment, the remission group showed lower levels of FBG (WMD, -0.45) and PBG (WMD, -1.19), along with higher levels of LnHOMA-B (WMD, 0.23). Additionally, the remission group showed greater improvements in PBG (WMD, -1.85) and LnHOMA-IR (WMD, -0.20; $p < 0.01$). Conclusion: CSII treatment maintained more than 50% drug-free remission rates within 12 months of follow-up. Certain clinical characteristics of participants can predict remission outcomes, including BMI, FBG, PBG, LnHOMA-IR, and LnHOMA-B.

Keywords: Continuous subcutaneous insulin infusion, remission rate, type 2 diabetes, predictor, meta-analysis

Introduction

Type 2 diabetes is chiefly caused by genetic and environmental factors. There are two main pathological defects in the disease, insulin resistance and β-cell dysfunction [1]. The natural history of the disease is characterized by progressive deterioration of β-cell function over time, a pathological process that occurs regardless of lifestyle and existing pharmacological interventions [2, 3]. Therefore, typical clinical treatment of this disease consists of the sequential addition of anti-diabetic drugs. Insulin therapy is often considered ultimately when functional β-cell capacity deteriorates to the point where glycemic control can no longer be achieved without exogenous insulin supplementation [4].

There is mounting evidence, however, indicating that continuous subcutaneous insulin infusions [CSII] used in the early stages of type 2 diabetes improve β-cell function and insulin resistance, resulting in an extended period of glycemic remission. For example, drug-free remission rates after 1 year were significantly higher in the CSII group (51.1%), compared to those in the oral hypoglycemic agents group (26.7%), according to a randomized controlled trial [5]. To date, some clinical trials have dem-

onstrated that CSII decidedly improves drug-free remission rates in newly diagnosed type 2 diabetes patients. The current meta-analysis was conducted to assess remission rates of patients treated with CSII, aiming to identify predictors associated with remission outcomes.

Methods

Literature search

This meta-analysis included clinical trials that assessed remission rates of CSII in type 2 diabetes mellitus patients. Electronic databases, including MEDLINE (via PubMed), the Cochrane Library, and EMBASE (via OvidSP), were searched for clinical trials using specific terms, including ('insulin' OR 'continuous subcutaneous insulin infusion' OR 'intensive insulin therapy') AND 'Type 2 diabetes' AND 'Remission'. Reference lists were manually checked for identified reports and relevant reviews.

Inclusion criteria: (1) Conducted in adults aged 18 years or older, with newly-diagnosed type 2 diabetes mellitus; (2) Patients treated with CSII therapy; and (3) Reported remission rates. If studies that had more than one interventional group, only the arm that received CSII therapy was analyzed. Exclusion criteria: (1) Number of included patients was less than 50; (2) Duration of follow-ups was shorter than 1 year; and (3) Duplicate reports for the same studies.

Data extraction and quality assessment

Two reviewers, independently, screened all titles and abstracts. They investigated full texts according to inclusion criteria, independently extracting data using standardized data extraction sheets. Divergences were resolved by consensus. Information extracted included study characteristics (first author's name, year of publication, study design, execute time, duration of follow-up, enrolled number, and completed number) and clinical characteristics of remission and non-remission groups (age, sex, body mass index [BMI], HbA1c, fasting blood glucose [FBG], postprandial blood glucose [PBG], insulin resistance LnHOMA-IR, β-cell function LnHOMA-B, and acute insulin response [AIR]).

Risk of bias was examined according to Preferred Reported Items for Systematic Reviews and Meta-analysis (PRISMA) recommendations. Study quality assessment addressed selection bias, description of losses or exclusions, and assessment of efficacy.

Statistical analysis

Identifying predictors associated with remission outcomes, this study compared clinical characteristics between remission and non-remission groups, including age, BMI, HbA1c, FBG, PBG, LnHOMA-IR, LnHOMA-B, and AIR. For age and BMI, only the baseline was compared. For other clinical characteristics, values at baseline, after CSII, and changes were compared.

Pooled outcomes were weighted mean differences (WMD) with associated 95% confidence intervals (CI). Inverse variance statistical methods and fixed-effects analysis models were used to calculate pooled effects sizes. I^2 testing was conducted to assess the magnitude of heterogeneity between studies, with values higher than 50% deemed to have high heterogeneity. A random-effects model was used to prove the robustness of analysis results. As a rule of thumb, tests for funnel plot asymmetry should only be used when there are at least 10 studies included in the meta-analysis. When there are fewer studies, the power of the tests is too low to distinguish chance from real asymmetry. Thus, publication bias was not tested in the current meta-analysis.

Results

A total of 446 studies were identified through electronic search methods. Of these, 433 were excluded based on the title and abstract, leaving 13 studies for further assessment. Five studies fulfilled the inclusion criteria, providing data for 550 participants [5-9]. The study selection process is shown in **Figure 1**.

Table 1 provides general information concerning included studies. These 5 studies were published between 2004 to 2017 [5-9]. In these studies, the patients were given CSII therapy for 14-21 days and followed-up for 1-2 years. Of the 550 patients that completed CSII treatment, 455 patients accomplished 1-year follow-ups, with a dropout rate of 17.3%. Patients included in this systematic review had a mean baseline HbA1c of 9.8-11% and mean baseline

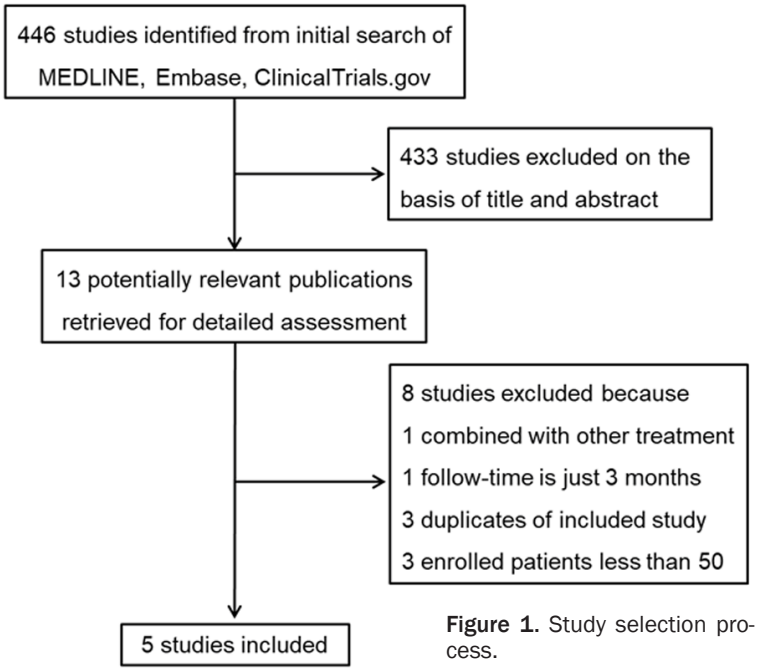

Figure 1. Study selection process.

BMI of 25.1-25.3 kg/m^2. For most enrolled patients, excellent blood glucose control was achieved in 3-7 days. **Table 2** shows the risk of bias in included studies. All studies reported adequate efficacy of CSII therapy (indicating that the study assessed glycemic remission rates of participants receiving CSII treatment). The dropout rate of these studies ranged from 3.8% to 21.3%.

Figure 2 shows remission rates of CSII at different follow-up times. Five studies with 527 patients were included in remission rate analysis [5-9]. Pooling the data of these studies, the proportion of participants with long-term drug-free remission was 72.0% (177 of 246 patients) at 3 months of follow-up, 62.5% (140 of 224 patients) at 6 months, 50.4% (243 of 482 patients) at 12 months, and 37.1% (33 of 89 patients) at 24 months.

Three studies compared clinical characteristics between remission and non-remission groups [6-8]. They defined the remission group as patients that had long term glycemic control > 12 months, without medication. The non-remission group was defined as patients that relapsed within 12 months. A total of 286 patients (remission group 150, non-remission group 136) were enrolled for analysis of predictors associated with remission outcomes.

Compared with the non-remission group, the remission group showed significantly higher baseline BMI (WMD, 0.78; 95% CI, 0.03 to 1.53; $p = 0.04$), LnHOMA-IR (WMD, 0.17; 95% CI, 0.05 to 0.29; $p < 0.01$), and LnHOMA-B (WMD, 0.22; 95% CI, 0.06 to 0.37; $p < 0.01$). After CSII treatment, the remission group had lower levels of FBG (WMD, -0.45; 95% CI, -0.68 to -0.22; $p < 0.01$) and PBG (WMD, -1.19; 95% CI, -1.66 to -0.72; $p < 0.01$), along with higher levels of LnHOMA-B (WMD, 0.23; 95% CI, 0.09 to 0.37; $p < 0.01$). Moreover, the remission group showed greater improvements in PBG (WMD, -1.85; 95% CI, -3.07 to -0.63; $p < 0.01$) and LnHOMA-IR (WMD, -0.20; 95% CI, -0.33 to -0.07; $p < 0.01$). Comparison results are shown in **Figure 3**.

I^2 testing was conducted to assess the magnitude of heterogeneity for these comparisons. There were four comparisons with significant heterogeneity, including HbA1c, FBG, PBG after CSII therapy, and improvements in LnHOMA-B (I^2 = 57, 56, 74, and 52%, respectively). However, these results were stable. No significant changes were noted, according to the random-effects model used to test robustness.

These three trials also reported differences in acute insulin response (AIR) between remission and non-remission groups [6-8]. This parameter together could not be pooled together, as two studies presented data as medians and interquartile ranges. Briefly, the remission group showed better levels and greater improvements in AIR after CSII treatment.

Discussion

The number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014. The worldwide prevalence of diabetes among adults over 18 years of age has risen from 4.7% to 8.5%. Prevalence of diabetes has continually risen, rapidly, in developing countries, especially in China and India. This may be due to population growth, aging, lack of physi-

Table 1. Characteristics of included studies

Author	Year	Enrolled number	Completed number	Age	Men (%)	BMI (kg/m^2)	HbA1c (%)	CSII treatment (day)	Achieving glycemic control (day)	Follow-up (year)
Li Y [7]	2004	126	113	48.6	61.9	25.1 ± 3.7	10.0 ± 2.2	14	6.3	2
Weng J [5]	2008	133	124	50.0	66.2	25.1 ± 3.0	9.8 ± 2.3	14	4.0	1
Chen A [6]	2012	187	118	51.6	66.1	25.0 ± 3.0	11.0 ± 2.1	14-21	3-5	1
Liu L [8]	2015	104	100	48.3	68.3	25.3 ± 3.0	10.9 ± 2.1	14	3.5	1
Shi X [9]	2017	63	60	45	NA	24.7 ± 3.2	10.2 ± 2.8	21	6.5	2

NA, not available; BMI and HbA1c are shown as mean ± standard deviation.

Table 2. Assessment of studies for risk of bias

Author	Selection bias	Efficacy assessed	Stopped early	Dropout rate (%)	Outcome assessment accurate
Li Y [7]	No	Yes	No	10.3	Yes
Weng J [5]	No	Yes	No	6.8	Yes
Chen A [6]	No	Yes	No	21.3	Yes
Liu L [8]	No	Yes	No	3.8	Yes
Shi X [9]	No	Yes	No	4.8	Yes

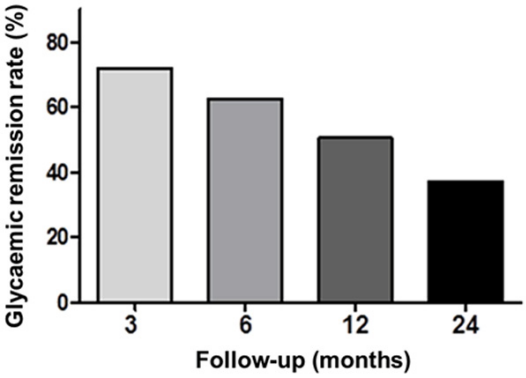

Figure 2. Remission rates of CSII therapy at different follow-up times.

cal activity, and obesity [10]. In 2010, a national study including 46,239 adults reported prevalence rates of diabetes among Chinese people. This study indicated that age-standardized prevalence levels of total diabetes and prediabetes were 9.7% and 15.5% [11]. Given the younger age of incidence, diabetes is not only a major public health problem, but also an economic problem. It has been predicted that the majority of people with diabetes living in developing countries will be aged 45-64 years by 2030, with a loss of some of their most productive years to disease, disability, or death [12]. Therefore, prevention, detection, and treatment of diabetes are very important issues.

In 1997, Ilkova first reported the possibility of CSII therapy resulting in drug-free remission rates in recently diagnosed type 2 diabetes patients [13]. Afterward, many trials were performed, evaluating remission rates associated with CSII therapy in patients recently diagnosed with type 2 diabetes patients. In the current research, pooled results of five trails with 482 patients showed that the proportion of participants in drug-free remission was 72.0% at 3 months of follow-up, 62.5% at 6 months, 50.4% at 12 months, and 37.1% at 24 months. Additionally, two of these included trials compared remission rates of CSII with other treatments. Remission rates were significantly higher in both CSII and multiple daily insulin injection (MDI) groups (51.1% in CSII and 44.9% in MDI) than in the oral hypoglycemic agents group (26.7%) at 1-year follow-up [5]. However, the CSII only group showed lower remission rates, compared with the CSII + exenatide group at both 1-year (39.7% vs 71.2%) and 2-year (34.9% vs 56.1%) follow-ups [9].

The current study analyzed clinical characteristics associated with remission outcomes of CSII on type 2 diabetes. Pooled results from three trials indicated that remission groups had: (1) Higher baseline BMI, LnHOMA-IR, and LnHOMA-B; (2) Lower levels of FBG and PBG, along with higher levels of LnHOMA-B after CSII treatment; and (3) Better improvement in PBG and LnHOMA-IR. These three trials also indicated that remission groups had better levels and greater improvement in AIR after CSII treatment.

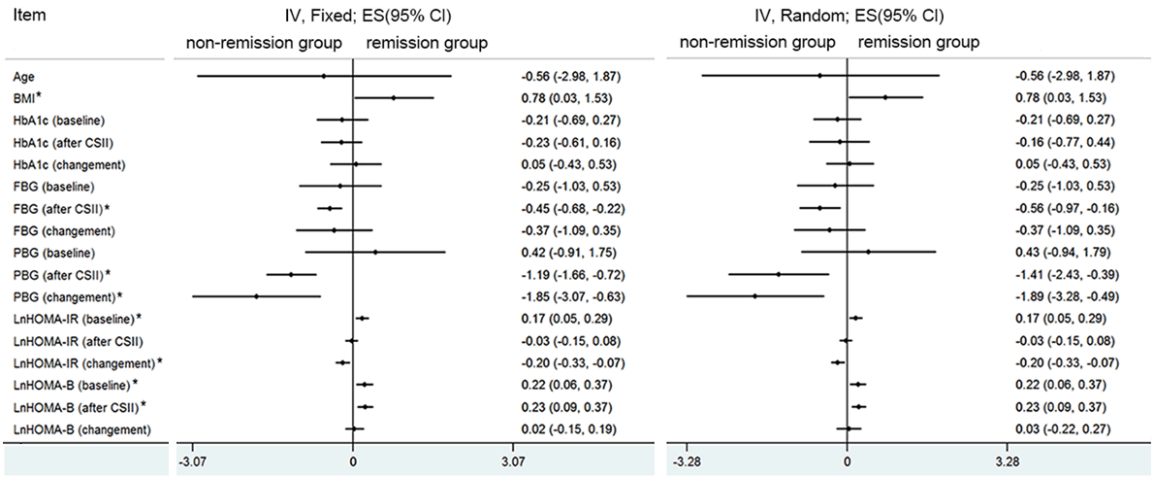

Figure 3. Clinical characteristics between remission and non-remission groups. IV, Inverse variance statistical method; Fixed, fixed effect analysis model; Random, Random-effects analysis model; ES, effect size; *significant differences between remission groups and non-remission groups ($p < 0.05$ or $p < 0.01$).

Other than these predictors, there may be other parameters associated with long-term drug-free remission, including: (1) Attitude, patients remaining in drug-free remission had higher scores in positive attitudes, (belief in) importance of care, care ability, self-care adherence, and less negative attitudes [6]; (2) Decrement of total daily insulin dose after euglycemia was achieved (ΔTDD). More patients in the upper ΔTDD tertile (≥ 25.0 IU) remained in glycemic remission, compared with those in the lower tertile (≤ 13.5 IU) (91.4% vs. 65.6%, P = 0.004) [14]; and (3) Acute glucagon response (AGR), similar with LnHOMA-IR. The remission group showed higher levels of AGR at baseline and lower levels after CSII treatment [15].

However, there were several limitations to the current study. First, only a few trials evaluated different remission rates between CSII and other treatments. Based on the results of two randomized control trials, CSII groups showed similar remission rates, compared with MDI groups. They showed higher rates, compared with oral hypoglycemic agent groups, and lower rates, compared with the SCII + exenatide group. However, more randomized control trials are necessary to evaluate remission rates of different therapies. Second, the sample size was relatively small. There were only three trials with 286 patients included in the predictor analysis. The small number of patients decreased the reliability of final conclusions. Third, certain specific parameters could not be pooled in the meta-analysis. This was due to different data forms reported and the limitation of studies included, including AIR, attitudes toward diabetes, ΔTDD, and AGR. Fourth, all included studies were performed in China. Thus, the results might not be generalizable to other populations, considering ethnic differences in obesity or fat deposition. Asians typically have a higher prevalence of diabetes than white people, when matched for BMI and waist circumference [16].

In conclusion, the current study is the first to evaluate remission rates and predictors of continuous subcutaneous insulin infusions in type 2 diabetes. CSII treatment maintained more than 50% drug-free remission rates within 12 months of follow-up. Certain clinical characteristics of participants can predict drug-free remission outcomes, including BMI, FBG, PBG, LnHOMA-IR, and LnHOMA-B.

Disclosure of conflict of interest

None.

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