A systematic review and meta-analysis of interventions to preserve insulin-secreting β-cell function in people newly diagnosed with type 1 diabetes

Narendran, Parth; Tomlinson, Claire; Beese, Sophie; Sharma, Pawana; Harris, Isobel; Adriano, Ada; Maggs, Fiona; Burrows, Martin; Nirantharakumar, Krishnarajah; Thomas, Neil; Price, Malcolm J; Andrews, Robert C; Moore, David J

DOI:
10.1111/dme.14730

License:
Other (please specify with Rights Statement)

Document Version
Peer reviewed version

Citation for published version (Harvard):
Narendran, P, Tomlinson, C, Beese, S, Sharma, P, Harris, I, Adriano, A, Maggs, F, Burrows, M, Nirantharakumar, K, Thomas, N, Price, MJ, Andrews, RC & Moore, DJ 2022, 'A systematic review and meta-analysis of interventions to preserve insulin-secreting β-cell function in people newly diagnosed with type 1 diabetes: results from intervention studies aimed at improving glucose control', *Diabetic Medicine*, vol. 39, no. 1, e14730. https://doi.org/10.1111/dme.14730

A systematic review and meta-analysis of interventions to preserve insulin-secreting beta cell function in people newly diagnosed with type 1 diabetes: results from intervention studies aimed at improving glucose control

Dr Parth Narendran*^, Institute of Immunology and Immunotherapy, University of Birmingham, and University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK, B15 2TT. (ORCID ID: 0000-0002-4583-8793)

Dr Claire Tomlinson*, Institute of Applied Health Research, University of Birmingham, Birmingham, UK, B15 2TT

Miss Sophie Beese*, Institute of Applied Health Research, University of Birmingham, Birmingham, UK, B15 2TT. (ORCID ID: 0000-0001-6329-0779)

Mrs Pawana Sharma, Institute of Applied Health Research, University of Birmingham, Birmingham, UK, B15 2TT. (ORCID ID: 0000-0001-6727-5998)

Miss Isobel Harris, Institute of Applied Health Research, University of Birmingham, Birmingham, UK, B15 2TT. (ORCID ID: 0000-0001-8125-3832)

Miss Ada Adriano, Institute of Applied Health Research, University of Birmingham, Birmingham, UK, B15 2TT. (ORCID ID: 0000-0001-8894-9007)

Mrs Fiona Maggs, Patient public representative

Mr Martin Burrows, Patient public representative

Dr Krishnarajah Nirantharakumar, Institute of Applied Health Research, University of Birmingham, Birmingham, UK, B15 2TT (ORCID ID: 0000-0002-6816-1279)

Professor G. Neil Thomas, Institute of Applied Health Research, University of Birmingham, Birmingham, UK, B15 2TT. (ORCID ID: 0000-0002-2777-1847)

Dr Malcolm J Price, Institute of Applied Health Research, University of Birmingham, Birmingham, UK, B152TT. (ORCID ID: 0000-0002-7352-3027)

Dr Robert C Andrews*, University of Exeter Medical School, Exeter, UK, EX1 2HZ (ORCID ID: 0000-0003-4939-1738)

Dr David J Moore*^, Institute of Applied Health Research, University of Birmingham, Birmingham, UK, B15 2TT (ORCID ID: 0000-0002-4163-4080)

*joint first or joint last
^corresponding/guarantors (Parth Narendran, Institute of Immunology and

Immunotherapy, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, B15 2TT. 0121 414 3006. p.narendran@bham.ac.uk)

Word Count: 4407 (excluding abstract, tables, figure legend, references, funding, contributions, acknowledgements)
Number of tables: 2
Number of figures: 3

Conflicts of Interest: None declared

Acknowledgements: This paper presents independent research funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number PB-PG-0317-20046). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

The authors wish to thank the members and management of the Juvenile Diabetes Research Foundation (JDRF) who gave up their valuable time to participate in group meetings to provide the child and adolescent patient and carer perspectives on living with type 1 diabetes in relation to the aims of this research, and Information specialists, Susan Bayliss and April Coombe, for their invaluable guidance and activities on searching databases.

Funding National Institute of Health Research - Research for Patient Benefit

Contribution of authors: PN conceived the research idea. PN and DM are joint principle investigators providing clinical and methodological leadership respectively. CS, PS, PN, RA, MP and DM drafted the protocol with input from all authors. CS ran searches. CS, PS, SB, IH, AA, FM, MB undertook study selection, data extract and or risk of bias assessment. SB undertook final data checking. CS, SB, PS, amalgamated data and undertook data synthesis and meta-analysis. MP oversaw the meta-analyses and all statistical matters. RA provided detailed clinical input and guidance at all stages, including contextualisation of findings and the discussion. FG and MB provided the adult patient perspective on living with type 1 diabetes. KN and NT provided methodological and clinical guidance. PN, SB, RA, DM, MP drafted this manuscript. All authors contributed to editing the manuscript.

Abstract

Aims: Type 1 diabetes is characterised by the destruction of pancreatic beta cells. Significant levels of beta cells remain at diagnosis. Preserving these cells improves glucose control and protects from long-term complications. We undertook a systematic review and meta-analyses of all randomised controlled trials (RCTs) of interventions to preserve beta cell function in people newly diagnosed with type 1 diabetes. This paper reports the results of interventions for improving glucose control to assess whether they preserve beta cell function.

Methods: Searches for RCTs in MEDLINE, Embase, Cochrane CENTRAL, ClinicalTrials.gov and WHO International Clinical Trials Registry. Eligible studies included newly diagnosed type 1 diabetes patients, any intervention to improve glucose control and at least one month of follow-up. Data were extracted using a pre-defined data-extraction sheet with 10% of extractions checked by a second reviewer.

Results: Twenty-eight studies with 1,662 participants were grouped by intervention into six subgroups (alternative insulins, subcutaneous and intravenous insulin delivery, intensive therapy, glucose sensing, adjuncts). Only three studies demonstrated an improvement in glucose control as well as beta cell function. These interventions included intensive insulin therapy and use of an alternative insulin.

Conclusions: This is the largest comprehensive review of RCTs in this area. It demonstrates a lack of robust evidence that interventions to improve glucose control preserve beta cell function in new onset type 1 diabetes, although analysis was hampered by low quality evidence and inconsistent reporting of studies. Development of guidelines to support the design of trials in this field is a priority.

Key Words: Type 1 diabetes – Systematic review – Beta cell function – Meta-analysis

Research in Context

What is already known about this subject?

1. Type 1 diabetes is characterised by autoimmune destruction of insulin secreting beta cells.
2. Preserving residual beta cells present at diagnosis has clinical benefits.
3. No formal unbiased synthesis of the evidence on effectiveness of interventions to preserve beta cell loss has been undertaken.

What has this research found?

1. There is a lack of robust evidence that interventions to improve glucose control preserve beta cell function in new onset type 1 diabetes
2. Studies in this area are hampered by low quality evidence and inconsistent reporting
3. Formal guidelines are required for the design of studies of beta cell preservation

What are the implications of the research?

1. Until formal evidence is obtained that glucose control preserves beta cell function in people with newly diagnosed type 1 diabetes, treatment algorithms and efforts should prioritise other interventions

Introduction

Type 1 diabetes is a chronic condition resulting from the autoimmune destruction of pancreatic insulin secreting beta cells leading to insulin insufficiency[1]. This beta cell loss leading up to diagnosis with type 1 diabetes is gradual and continues after diagnosis. At diagnosis a significant number of beta cells remain, thus enabling relatively lower doses of exogenous insulin replacement to limit glucose variability and hypoglycaemia. Persistence of residual beta cells associates with better glucose control, reduced glucose variability and fewer microvascular complications[2].

Over the last four decades a variety of therapies have been tried in people newly diagnosed with type 1 diabetes to try and slow or stop beta cell loss[3]. No formal overarching and unbiased synthesis of the evidence on the effectiveness of these therapies in new onset type 1 diabetes has been undertaken. We have undertaken such a systematic review with the overarching aim to determine which therapies warrant further investigation solely or in conjunction as combination therapy for beta cell preservation in the context of newly diagnosed type 1 diabetes. This paper reports the findings relating to the effectiveness of interventions aimed at improving glucose control in patients newly diagnosed with type 1 diabetes. In this regard, we define improved glucose control as lower glycated haemoglobin or less variable (as defined by time in range or other suitable measure). We will report the findings relating to the effectiveness of non-glucose control-based interventions in future publications.

The rationale for glucose control preserving beta cell function comes from clinical observations that glucose control and beta cell function are often associated[4, 5], and from ex-vivo studies demonstrating that high glucose is detrimental to beta cell health ("glucose toxicity")[6, 7]. However, the observation that glucose control associates with beta cell function does not prove causation. The most widely cited evidence for causation comes from the Diabetes and Complications Trial (DCCT)[8]. which tested whether glucose control prevents the complications of type 1 diabetes. A retrospective analysis of 303 participants who had less than five-year duration of type 1 diabetes[9] revealed that beta cell function was significantly better in those participants with intensive glucose control for the subsequent four of six years of follow-up. Whilst this analysis supports intensive glucose control preserving beta cell function, important baseline differences and retrospective analysis of a subgroup of prospectively collected data is insufficient evidence on which to base clinical practice.

We formally explore the evidence of interventions for improving glucose control to determine whether they preserve beta cell function in new onset type 1 diabetes through a comprehensive review of published literature. The standard measure of beta cell function is the C-peptide molecule. This is a fragment of the pro-insulin molecule that is cleaved during the processing of the insulin precursor and which can be measured through blood or urine-based assays following either a fast or meal

stimulation[10] (Figure 1). We therefore undertook a systematic review of randomised controlled trials of interventions aimed at improving glucose control in patients newly diagnosed with type 1 diabetes that report C-peptide and where patient follow-up was at least 1-month from initiation of the intervention.

(Figure 1 here)

Methods

Data Sources and Searches

The systematic review methods were guided by current best practice[11], the protocol was registered on PROSPERO, the international database of prospectively registered systematic reviews, (registration code: CRD42018107904) and the review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[12].

Bibliographic databases searched included MEDLINE, Embase, Cochrane CENTRAL, trials registries (Clinical Trials.gov and WHO International Clinical Trials Registry). This was augmented by citation checking of included studies and relevant systematic reviews.

Bibliographic databases were searched using a combination of index and free text terms for type 1 diabetes. A study design filter[13] with maximised sensitivity for RCTs was used in MEDLINE and Embase). Searches of other sources used free text terms for type 1 diabetes. The MEDLINE search strategy is detailed in Supplemental Table 1.

Databases were searched from inception to September 2019. Searches were not restricted by language or publication date.

Study Selection

Study eligibility was defined as follows:

Population: Adults and children diagnosed with type 1 diabetes within the previous three years

Setting: Any

Intervention: Therapies aiming to improve glucose or metabolic control or preserve beta cell function. These included improving control through route of insulin delivery, intensity of therapy, use of adjunctive therapies or use of insulin infusion and glucose sensing devices.

Comparator: Any; including different route or mode of administration, different frequency or dose of insulin such that dose and delivery method comparison studies were included.

Outcomes: Beta-cell function through any measurement of C-peptide

Secondary outcomes for the review were diabetes related measures (insulin doses, HbA1c), adverse effects, weight, compliance with treatment, and quality of life (QoL)

Study design: RCTs with at least 1-month follow-up.

Publication type: Journal articles, conference abstracts and trial registration records.

Search results were entered into Endnote (X9 Clarivate Analytics) and duplicate records were removed automatically and manually. Titles and abstracts were screened for relevance. Full text copies of relevant articles were assessed against the inclusion criteria. Studies meeting all selection criteria were included. Reasons for exclusion of articles were recorded. Study selection was conducted by two reviews independently with disagreements resolved by discussion, involving a third reviewer if required.

Data extraction and Quality Assessment

Data were extracted using a bespoke and piloted sheet in MS Excel by a single reviewer with 10% checked by a second reviewer, with additional checking during analysis. For each study, the following data were sought: study design (including: participant allocation, methods of blinding, sample size; participations (including participant inclusion and exclusion criteria, methods of recruitment, participant characteristics, length of follow-up, completeness of follow-up and reasons for drop outs); intervention/comparator (including: type, mode of delivery, dose, duration adherence); outcomes (outcome, measurement method, time points; participant numbers at each time point; type of analysis (ITT/per protocol, data and associated uncertainty, statistical methods employed, imputation method of missing data). Detailed descriptions of how C-peptide was measured in each study including fasting/stimulated and method of stimulation, time points of measurement or duration of continuous measurement, units, and details on estimation of area under the curve measures). Where possible C-peptide data were converted to nmol/L. Authors of relevant abstracts were contacted for further information and data.

Data were taken from text or tables where possible, with data read from graphs as a secondary option using software[14]. Means and standard deviations were extracted for all outcomes, missing standard deviations were calculated from standard errors or confidence intervals where possible.

Risk of bias in included studies was assessed using the Cochrane Risk of Bias tool[15].

Data Synthesis and Analysis

Included studies were grouped by intervention and comparator and a narrative synthesis was undertaken of all studies. Within each grouping, data for each relevant outcome and the method of assessment were considered. Where reported, outcomes were assessed at 6, 9, 12, 18, 24 and 36 months after initiation of intervention.

Suitability for meta-analysis was assessed based on clinical and methodological homogeneity for each outcome (C-peptide, HbA1c, insulin dose), measurement method and type of data for each intervention-comparator dyad. Where meta-analysis was deemed appropriate the random effects model was used. Heterogeneity is reported using I^2 and tau-squared statistics[16] where appropriate. For each analysis, data were prioritised by type, (i) change scores from baseline for each group, calculated using an appropriate model (e.g. ANCOVA), (ii) end point data/final scores for each group at each reported time point during follow-up, (iii) change scores from baseline with no information on methods of calculation. Mean differences between arms were used where possible. Forest plots were created for each meta-analysis undertaken. Plots including all pooled estimates are present for each outcome.

Each type of C-peptide data (2-hour AUC, 4-hour AUC, maximum stimulation, fasting) and method of C-peptide stimulation (glucagon stimulated, meal stimulated, glucose stimulated or not stated) were reported separately. Nmol/L was the preferred unit for reporting C-peptide. HbA1c is presented as both mmol/mol and percentages, and insulin dose as units/kg/day.

Results

25,069 records were identified from the searches (Figure 2 PRISMA flowchart). Following removal of duplicates, screening and selection, 135 studies (reported in 195 articles) were included in the wider review on all therapies for beta cell preservation. Of these, 28 studies (37 articles) were related to interventions aiming to improve glucose control. There were 68 relevant ongoing or unpublished studies of which four related to glucose control interventions (Supplemental Table 2).

(Figure 2 PRISMA flowchart here)

The studies were categorised into six subgroups by intervention type. Study characteristics are outlined in the table of characteristics (Table 1). Figure 3 shows the summary of meta-analyses findings for each intervention subgroup for HbA1c, Insulin dose, C-peptide and C-peptide AUC at each follow-up time point. The meta-analyses from which the summary pooled estimates are take can be found in the Supplemental Figures.

(Table 1. Study Characteristics here.)

(*Figure 3. Summary plots of meta-analyses findings for each intervention subgroup for each primary outcome at each follow-up time point here.)*

Subgroup 1: Alternative insulin preparations (4 studies, 415 participants)

This group involved studies where a newer insulin preparation was compared with standard care. There were a total of four studies[17-20] and 415 participants, with only one of the studies including fewer than 100 participants[19]. All studies involved porcine, bovine, soluble, NPH or rapid acting insulins. The newer rapid acting insulins which are now commonly used in clinical practice was used as a comparator in only one study[19]. Of the four studies only three reported insulin dose data but with no consistency in the reporting statistics to allow for meta-analysis. No consistent dose reduction was seen over the time points reported. Whilst all four studies reported HbA1c, there was also inconsistency in reporting data within and across time points, and this hampers interpretation. Data were available from three studies for 12 months follow-up with meta-analyses of these indicating a small benefit with alternate preparations (-4.2 mmol/mol (-0.39%) (95% CI -8.2 (0.75%) to -0.3 (0.03%); p=0.03; n=three studies) [17, 19, 20].However, this was driven by the effect of a single study for which no other data are available at any other time point. Neither of the other two studies indicate a benefit at 12 months or six months (though confidence intervals do not rule this out), and there was no longer term data from any studies with which to corroborate this effect. There was no convincing data of a

difference between insulin preparations on preserving C-peptide across the measurement methods used. One study[17] did demonstrate a higher fasting C-peptide than baseline at nine months in the intervention group that was not present in the control group. However, this was not maintained nor replicated by the other studies, with data favouring control at other time points (mean difference at 12 months -0.06 nmol/L 95% CI -0.10 to -0.01; p=0.02 n=two studies). Two studies could not be combined due to inconsistency of reporting statistics, but both showed no clear differences between the alternative insulin and control at 12 months. No improvements were seen in other studies reporting meal stimulated and glucagon stimulated C-peptide.

Only two of the four studies reported adverse events (Supplemental Table 3). By 12 months follow up with rapid compared to regular insulin there were only mild hypoglycaemic events reported (0.3 vs 0.8 events per week)[19]. With porcine insulin compared to bovine/porcine mixed insulin the portions experiencing a severe hypoglycaemic event were not small with higher rates with pure porcine insulin (53% vs 40%)[17]

.

Subgroup 2: Continuous subcutaneous insulin infusion (CSII) (8 studies, 283 participants)

This group involved studies where insulin was delivered through different devices. All studies compared continuous subcutaneous insulin infusion (CSII) to pen injection. Whilst the delivery device differed, the subcutaneous route remained consistent in both arms in all studies. There were a total of eight studies [21-28] and 283 participants with all but two studies having 30 or fewer participants. Meta-analysis of six studies[21-24, 26, 29] at 12 months showed no evidence of a difference in insulin dose between CSII and pen delivery (mean difference 0.01 units/kg/day 95% CI -0.04 to 0.06; p=0.75). Levels of HbA1c reduced from baseline with both delivery modalities, with no evidence of a difference in effect between them at 12 months (mean difference -0.1mmol/mol (-0.01%) 95% -15.8 (-1.45%) to 15.5 (1.42%); p=0.98; n=five studies)[21-23, 25, 26]. At 18 and 24 months a benefit of CSII over pen was found but this was due to a single study[23]. This study showed a benefit for CSII over pen at all follow up times however baseline values for pen were not given and therefore the possibility of baseline imbalances giving rise to the effect on HbA1c in this study cannot be ruled out. Again there was no convincing data at any follow up time points (maximum 24 months) of a difference between modes of insulin delivery on preserving C-peptide across the measurement methods used; except a small difference in maximum meal stimulated level in two small studies[24, 26] at 12 months favouring CSII (mean difference 0.18 nmol/L 95% CI 0.07 to 0.28; p=0.001). One study[27] did not report C-peptide, although it had been measured, but did state that

there was no difference between the groups at 12 or 24 months follow up for fasting levels.
No study in this group reported meal stimulated C-peptide as area under curve.
Adverse events were not reported or poorly reported across the majority of studies. Hypoglycaemia was reported in four studies[21, 23-25] with no events or a small number of events occurring and no evidence of a difference between CSII and pen delivery.

Subgroup 3: Intravenous insulin delivery (3 studies, 87 participants)
This group involved studies where insulin was delivered by a different route. There were three studies[30-32] with 87 participants, two with fewer than 20 participants and one with 54 participants. All studies compared a period of intravenous insulin against subcutaneous pen injection. There was no evidence from meta-analyses of a difference in effect of intravenous insulin therapy compared to subcutaneous pen injection on insulin dose, HbA1c or C-peptide; despite some baseline imbalances between groups for some outcomes in some studies. Confidence intervals were generally wide. One study could not be included in any C-peptide meta-analyses due to varying measurement methods[33].
Adverse events were only reported in one of the three studies[30], with only one episode of hypoglycaemia leading to needing assistance reported by 12 months follow-up and therefore no detectable difference between routes of delivery.

Subgroup 4: Intensive insulin therapy (5 studies, 461 participants)

This group involved studies where intensive insulin therapy was compared against standard care. There were five studies with a total of 461 participants in this group[9, 34-37]; one of these studies was terminated early with only limited data for up to 6-months of follow-up reported[36]. The insulin formulation, route of administration and device used were largely similar across arms and they differed primarily by the support provided around insulin dose adjustment. The exception was the DCCT study[9] where escalation from multiple dose insulin injection therapy to continuous subcutaneous insulin delivery occurred in some participants. When looking across all follow up data up to 60 months meta-analyses suggest no evidence of reduction in insulin dose with intensive insulin therapy compared to usual care was seen although not all studies contributed data for this outcome beyond baseline and up to two studies only contributed to data at each follow up time. Also in two[34, 37] of the four studies[34-37] that reported baseline insulin dose there was considerable imbalance between intensive insulin and control arms. Only one of these studies contributed follow up data and there were no evidence of differences between the arms. HbA1c improved with both intensive insulin and usual care after baseline with no significant difference between arms at up to 12 months shown in meta-analyses though confidence intervals were wide. Beyond this time point data suggests a significant benefit of intensive therapy over usual care based on only two studies [9, 35]

(e.g. mean difference -17mmol/mol (-1.56%) 95% CI -32.9 (-3.01%) to -1.1 (-0.10%); p=0.04 at 36 months).
C-peptide was variably reported which limited the possibility for combining data, resulting in study level descriptions being used. In Linn[35] a significant benefit in glucagon stimulated C-peptide of intensive therapy over usual care was found after 24 months extending to maximal follow up at 60 months[35]. Wang[37] only presented one year of follow-up and showed no significant difference in fasting C-peptide. Madsbad[34] reported no significant differences between the groups at any timepoints after 14 days and for up to 18 months for meal stimulated C-peptide. Conversely, participants in the DCCT study groups had similar C-peptide levels at baseline but those in the intensive therapy group had significantly higher meal stimulated C-peptide at follow ups for up to five years, eventually decreasing towards levels similar to those in the standard care group.

There was no evidence that intensive intravenous insulin therapy did not result in a reduction in insulin dose, improvement in HbA1c nor benefit on C-peptide measured either in the fasting state or following stimulation. Four of the five studies reported adverse events[9, 35-37]. Shorter term studies demonstrated no hyperglycaemic or other adverse events. The DCCT and Linn studies both report a low level of events over five-six years reaching a doubling in events with intensive therapy compared to usual care (events over <3.5 mmol/l glucose (mean(SD)) 3.9% (0.7%) vs 2.2% (0.5) and rate of severe hypoglycaemia (6.6 episodes per 100 patient-years of follow up vs 3.0)[9, 35].

Subgroup 5: Additional use of glucose sensing (2 studies, 228 participants)

This group included studies where glucose sensing technology was used to support better glucose control. There were two studies [38, 39], enrolling a total of 228 participants, where continuous glucose monitoring systems were used in conjunction with CSII either as a hybrid closed loop or sensor augmented pump. The comparator was capillary glucose monitoring. Blinding of participants was not possible due to the mode of treatment. Meta-analysis shows no evidence of a difference between groups at 12 months follow up in insulin requirements (mean difference -0.04 units/kg/day 95% CI -0.10 to 0.02; p=0.22) or HbA1c (mean difference -1.1mmol/mol (-0.10%) 95% CI -4.8 (-0.44%) to 2.6 (0.24%); p=0.55). One of the two studies reported significantly greater insulin does with glucose sensing technology at nine-months follow-up but not at later time points. There was no convincing evidence of a difference in effect between glucose sensing and CSII on C-peptide. Adverse events were reported in both studies and the effect on hypoglycaemia was contradictory. In one study[38] there were no severe hypoglycaemic events within the short term (up to 12 months) or longer term (12-24 months) with glucose sensing, compared to four episodes and two episodes respectively with CSII. The other study[39] reported a single hypoglycaemic event which occurred in the sensing arm where the sample size was double that of CSII.

Subgroup 6: Adjunctive therapy (6 studies, 178 participants)
This group involved studies where sulphonylurea, glitazone, dipeptidyl peptidase DPP4 inhibitor or glucagon-like peptide 1 (GLP1) receptor agonist therapy was used in addition to insulin as adjunctive therapy with the aim of improving glucose control. Insulin administration was maintained in both arms across all studies.

For sulphonylurea adjunctive therapy, there were three studies with 75 participants[40-42] . Only one of the studies[40] reported on insulin dose but baseline imbalances between groups preclude meaningful interpretation. Meta -analysis of two studies[40, 42] indicated there was evidence of a difference between adjunctive treatment with sulphonylurea and control with regard to effect on HbA1c up to 12 months follow up (-5.7 mmol/mol (-0.52%) 95%CI: -16.4 (-1.5%) to 4.9 (0.45%); p=0.29). Although one of the two studies[42] did show a non-significant benefit with sulphonylurea at 6, 12 and 18 months. None of the three studies showed no evidence of a benefit of sulphonylurea over control on C-peptide.

Adverse events were either not reported or poorly reported; an episode of severe hypoglycaemia was reported in one study[41], but it was not clear in which group it occurred.

For glitazone adjunctive therapy, there was only one study with a total of 15 participants randomised to either insulin alone or insulin plus pioglitazone over 24 weeks[43]. The study only reported results for C-peptide preservation and there was no evidence for improvement with adjunctive therapy. Adverse events were reported and none were encountered.

For DPP inhibitor and/or GLP1 therapy there were two studies with 88 participants randomised to either usual care or a combination of sitagliptin and lansoprazole[44] , or usual care or exenetide or sitagliptin[45]. There was no evidence that adjunctive treatment with the combination of sitagliptin and lansoprazole compared to usual care reduces insulin dose, improves HbA1c, or preserves C-peptide at one year. There was weak evidence of a reduction in insulin dose and improvement in HbA1c when treated with sitagliptin alone[45]. However, the tiny sample size and baseline imbalance make it difficult to draw conclusions. Based on six participants, adjunctive treatment with exenetide compared to usual care did appear to reduce insulin dose and improve HbA1c at one year but there was no evidence of an associated improvement in C-peptide. Adverse events were reported and there appeared to be no difference in severe hypoglycaemic events across both studies. In one study[44], mild/moderate hypoglycaemia was noticeably higher in the intervention group (44 participants with 1190 events) than the control (19 participants with 424 events).

Risk of Bias

Reporting of methodological features to minimise bias was poor for the majority of studies (Table 2). Allocation concealment, random sequence generation, blinding to allocation for outcome assessment was frequently unclear or had a high risk of bias. Blinding of C-peptide outcome was unknown or low across most studies. Very few studies had consistently low risk of bias across the majority of domains. In addition of the 28 studies: 15 reported frequency of hypoglycaemia[9, 17, 19, 21, 23-25, 30, 35, 37-39, 41, 44, 45]; six adverse events[17, 23, 25, 36, 43, 44], three weight[19, 42, 45], one QoL[38] and one study compliance rates[44].

(Table 2. Risk of Bias here)

Discussion

This, the largest and most comprehensive systematic review of this subject area, demonstrates a lack of robust evidence that interventions to improve glucose control preserve beta cell function in new onset type 1 diabetes. This is a notable statement given the general assumption in routine clinical practice for this is to be the case.

Many of the trials that wished to test the hypothesis that improved glucose control preserves beta cell function failed to demonstrate an improvement in glucose control. Therefore, any preservation in C-peptide in these studies cannot be attributed to glucose control. Conversely a number of studies that demonstrated an improvement in glucose control did not demonstrate a concurrent improvement in beta cell function[23, 45]. Of the ten studies[9, 17, 19, 20, 22, 23, 30, 35, 42, 45] that demonstrated an improvement in glucose control, three studies[9, 17, 35] also demonstrated an improvement in beta cell function. First, Asplin (1987)[17] reported an improvement in HbA1c that was associated with improved fasting C-peptide that was present at nine months but did not persist past this. This was a study comparing pure porcine compared to partially purified bovine/porcine insulin and where some of the baseline data were not available. Second, Linn (1996)[35] demonstrated an improved HbA1c associated with an improvement in glucagon-stimulated C-peptide, but only after three years of intensive therapy and this is on a relatively small study of 42 participants. Third, and in direct contradiction, the DCCT[9] demonstrates that intensive therapy improves HbA1c and this associates with a higher meal stimulated C-peptide; an effect that only lasted for four years. Whilst the Linn study is smaller than the DCCT study, the latter suffers from issues relating to post-hoc analysis previously outlined in the introduction.

The strengths of the review are the comprehensiveness of search, broad definition of what constitutes newly diagnosed type 1 diabetes and a thorough analysis following rigorous protocol driven methods[11]. This is particularly important given the

heterogeneity between studies with regard to intervention, comparator, C-peptide measurement and data reported. Unfortunately, data from some studies were not available despite contacting authors.

This review highlights poor consistency in trial design and reporting, in particular lack of reporting of risk of bias minimising features. Inconsistent measures of C-peptide (fasting, stimulated), mode of stimulation (glucagon, meal), and timing of C-peptide measurement makes meta-analysis of studies very challenging. These methodological and reporting issues underpin the lack of robust evidence identified in this review, and recent international efforts have been launched to try to address them[46]. The limited data often meant that confidence intervals were wide. Furthermore, only 54% of the studies reported frequency of hypoglycaemia[9, 17, 19, 21, 23-25, 30, 35, 37-39, 41, 44, 45]; 21% adverse events[17, 23, 25, 36, 43, 44], 11% weight[19, 42, 45], and only one study each reported on quality of life[38] and compliance rates[44]. Weight is a key determinant of insulin resistance and thus can affect C-peptide. Rates of adverse events, effect on quality of life and acceptability are important in deciding whether an intervention should be adopted and will inform a combinatorial therapeutic approach to beta cell preservation. Whilst consensus statements have been proposed[47] formal core outcome sets will support the design of clinical trials, ensure that trials produce usable data, and allow combination of results across different studies.

Any future clinical trial to determine whether glucose control improves beta cell function will need to consider a number of issues over and above a standardised approach to clinical trial reporting. First, clinical guidelines recommend intensive glucose control from diagnosis[48]. Therefore, achieving a significant difference in glucose control will be more challenging. Second, good glucose control (as defined in this instance by lower glycated haemoglobin) reduces glycaemic exposure and the risk of long-term diabetic complications therefore all patients should be supported to achieve good glucose control from diagnosis. Therefore, there will be ethical implications to undertaking such a study. Third, there are currently ongoing studies[49, 50] comparing the use of close loop insulin delivery to standard care in new onset type 1 diabetes which may provide formal insight into this question.

In conclusion we found no robust trial evidence that interventions to improve glucose control preserve beta cell function in people newly diagnosed with type 1 diabetes. We also highlight that formal guidelines are required for the design of studies of beta cell preservation and that these guidelines should contain a core outcome set and agreement on how these core outcomes are measured.

References

1. DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. *Lancet* 2018; **391**:2449-2462.
2. Steffes MW, Sibley S, Jackson M, Thomas W. β-Cell Function and the Development of Diabetes-Related Complications in the Diabetes Control and Complications Trial. *Diabetes Care* 2003; **26**:832.
3. Skyler JS. Hope vs hype: where are we in type 1 diabetes? *Diabetologia* 2018; **61**:509-516.
4. Buckingham B, Cheng P, Beck RW, Kollman C, Ruedy KJ, Weinzimer SA*, et al.* CGM-measured glucose values have a strong correlation with C-peptide, HbA1c and IDAAC, but do poorly in predicting C-peptide levels in the two years following onset of diabetes. *Diabetologia* 2015; **58**:1167-1174.
5. Grönberg A, Espes D, Carlsson P-O. Better HbA1c during the first years after diagnosis of type 1 diabetes is associated with residual C peptide 10 years later. *BMJ Open Diabetes Research & Care* 2020; **8**:e000819.
6. Ebrahimi AG, Hollister-Lock J, Sullivan BA, Tsuchida R, Bonner-Weir S, Weir GC. Beta cell identity changes with mild hyperglycemia: Implications for function, growth, and vulnerability. *Molecular Metabolism* 2020; **35**:100959.
7. Weir GC. Glucolipotoxicity, β-Cells, and Diabetes: The Emperor Has No Clothes. *Diabetes* 2020; **69**:273-278.
8. Nathan DM, Group DER. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. *Diabetes care* 2014; **37**:9-16.
9. The Diabetes Control and Complications Trial Research Group. Effect of intensive therapy on residual beta-cell function in patients with type 1 diabetes in the diabetes control and complications trial. A randomized, controlled trial. *Annals of Internal Medicine* 1998; **128**:517-523.
10. Fu Z, Gilbert ER, Liu D. Regulation of insulin synthesis and secretion and pancreatic Beta-cell dysfunction in diabetes. *Curr Diabetes Rev* 2013; **9**:25-53.
11. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, . Cochrane Handbook for Systematic Reviews of Interventions. 2nd edn. Chichester (UK): John Wiley & Sons; 2019.
12. Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLOS Medicine* 2009; **6**:e1000097.
13. Lefebvre C ME, Glanville J,. Searching for studies. In: Higgins JPT GS, ed. *Cochrane Handbook for Systematic Reviews of Interventions* The Cochrane Collaboration 2011.
14. Rohatgi A. WebPlotDigitizer. 4.3 edn. Pacifica, California 2020. https://automeris.io/WebPlotDigitizer. Accessed September 2020.
15. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD*, et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**:d5928.
16. Deeks JJ HJ, Altman DG (editors),. Analysing data and undertaking meta-analyses. In: Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA,, ed. *Cochrane Handbook for Systematic Reviews of Interventions* 2020.
17. Asplin C, Raghu P, Clemons P. Randomized prospective trial of pure porcine and conventional bovine/porcine insulin. *Diabetes Care* 1987; **10**:337-342.
18. Marshall MO, Heding LG, Villumsen J, Akerblom HK, Baevre H, Dahlquist G*, et al.* Development of insulin antibodies, metabolic control and B-cell function in newly diagnosed insulin dependent diabetic children treated with monocomponent human insulin or monocomponent porcine insulin. *Diabetes Research* 1988; **9**:169-175.
19. Recasens M, Aguilera E, Morinigo R, Casamitjana R, Nicoletti F, Gomis R*, et al.* Insulin lispro is as effective as regular insulin in optimising metabolic control and preserving beta-cell function at onset of type 1 diabetes mellitus. *Diabetes Research & Clinical Practice* 2003; **60**:153-159.
20. Bang P, Salemyr J, Ekstrcm K, Pulkkinen MA, Carlsson-Skwirut C, Artqvist E. Children randomized to long acting insulin glargine or determir from diagnosis of type 1 diabetes mellitus

have lower HbA1C after one year as compared to those randomized to NPH insulin. *Pediatric Diabetes* 2011; **15)**:124.
21. Flores d'Arcais A, Morandi F, Beccaria L, Meschi F, Chiumello G. Metabolic control in newly diagnosed type 1 diabetic children. Effect of continuous subcutaneous infusion. *Hormone Research* 1984; **19**:65-69.
22. Edelmann E, Walter H, Biermann E, Schleicher E, Bachmann W, Mehnert H. Sustained normoglycemia and remission phase in newly diagnosed type I diabetic subjects. Comparison between continuous subcutaneous insulin infusion and conventional therapy during a one year follow-up. *Hormone & Metabolic Research* 1987; **19**:419-421.
23. De Beaufort CE, Houtzagers CMGJ, Bruining GJ, Aarsen RSR, Den Boer NC, Grose WFA*, et al.* Continuous subcutaneous insulin infusion (CSII) versus conventional injection therapy in newly diagnosed diabetic children: Two-year follow-up of a randomized, prospective trial. *Diabetic Medicine* 1989; **6**:766-771.
24. Shah SC, Malone JI, Simpson NE. A randomized trial of intensive insulin therapy in newly diagnosed insulin-dependent diabetes mellitus. *New England Journal of Medicine* 1989; **320**:550-554.
25. Pozzilli P, Crino A, Schiaffini R, Manfrini S, Fioriti E, Coppolino G*, 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 Technology & Therapeutics* 2003; **5**:965-974.
26. Thrailkill KM, Moreau CS, Swearingen C, Rettiganti M, Edwards K, Morales AE*, et al.* Insulin pump therapy started at the time of diagnosis: effects on glycemic control and pancreatic beta-cell function in type 1 diabetes. *Diabetes Technology & Therapeutics* 2011; **13**:1023-1030.
27. Ekstrom K, Skogsberg L, Fors H, Carlsson-Skwirut C, Bang P. Improved hepatic insulin sensitivity in children randomized to CSII treatment from onset of type 1 diabetes. *Hormone Research in Paediatrics* 2014; **1)**:32.
28. Lang Q, Ye B, Wang N, Li G. Therapeutic effect of different insulin injections on type 1 diabetes mellitus. *Biomedical Research (India)* 2017; **28**:9867-9870.
29. Guglielmi C, Williams SR, Del Toro R, Pozzilli P. Efficacy and safety of otelixizumab use in new-onset type 1 diabetes mellitus. *Expert opinion on biological therapy* 2016; **16**:841-846.
30. Schnell O, Eisfelder B, Standl E, Ziegler AG. High-dose intravenous insulin infusion versus intensive insulin treatment in newly diagnosed IDDM. *Diabetes* 1997; **46**:1607-1611.
31. Perlman K, Ehrlich RM, Filler RM, Albisser AM. Sustained normoglycemia in newly diagnosed type I diabetic subjects. Short-term effects and one-year follow-up. *Diabetes* 1984; **33**:995-1001.
32. Enander R, Bergdahl T, Adolfsson P, Forsander G, Gundevall C, Karlsson AK*, et al.* Intensive subcutaneous insulin therapy and intravenous insulin infusion at onset of diabetes preserve beta-cell function equally well in children. *Pediatric Diabetes* 2011; **15)**:69-70.
33. Enander R, Adolfsson P, Bergdahl T, Forsander G, Ludvigsson J, Hanas R. Beta cell function after intensive subcutaneous insulin therapy or intravenous insulin infusion at onset of type 1 diabetes in children without ketoacidosis. *Pediatric Diabetes* 2018; **19**:1079-1085.
34. Madsbad S, Krarup T, Faber OK, Binder C, Regeur L. The transient effect of strict glycaemic control on B cell function in newly diagnosed type 1 (insulin-dependent) diabetic patients. *Diabetologia* 1982; **22**:16-20.
35. Linn T, Ortac K, Laube H, Federlin K. Intensive therapy in adult insulin-dependent diabetes mellitus is associated with improved insulin sensitivity and reserve: a randomized, controlled, prospective study over 5 years in newly diagnosed patients. *Metabolism: Clinical & Experimental* 1996; **45**:1508-1513.
36. NCT00564018. Duration of The Honeymoon Phase of Type 1 Diabetes: A Comparison of Insulins Detemir, Glargine and NPH. https://ClinicalTrials.gov/show/NCT00564018.
37. Wang Y, Gong C, Cao B, Meng X, Wei L, Wu D*, et al.* Influence of initial insulin dosage on blood glucose dynamics of children and adolescents with newly diagnosed type 1 diabetes mellitus. *Pediatric Diabetes* 2017; **18**:196-203.

38. Kordonouri O, Pankowska E, Rami B, Kapellen T, Coutant R, Hartmann R*, et al.* Sensor-augmented pump therapy from the diagnosis of childhood type 1 diabetes: results of the Paediatric Onset Study (ONSET) after 12 months of treatment. *Diabetologia* 2010; **53**:2487-2495.
39. Buckingham B, Beck RW, Ruedy KJ, Cheng P, Kollman C, Weinzimer SA*, et al.* Effectiveness of early intensive therapy on beta-cell preservation in type 1 diabetes. *Diabetes Care* 2013; **36**:4030-4035.
40. Sanders R, Faro B, Stoler P, Mick GJ, McCormick KL. Adjunctive use of tolazamide in newly-diagnosed diabetic children. *Hormone & Metabolic Research* 1990; **22**:576-580.
41. Selam JL, Woertz L, Lozano J, Robinson M, Chan E, Charles MA. The use of glipizide combined with intensive insulin treatment for the induction of remissions in new onset adult type I diabetes. *Autoimmunity* 1993; **16**:281-288.
42. Fallucca F, Sciullo E, Maldonato A. Combined therapy with insulin and sulfonylurea for the treatment of new-onset insulin-dependent diabetes mellitus. *Hormon- und Stoffwechselforschung / Hormones et metabolisme [Hormone and metabolic research]* 1996; **28**:86-88.
43. Tafuri KS, Godil MA, Lane AH, Wilson TA. Effect of pioglitazone on the course of new-onset type 1 diabetes mellitus. *Journal of clinical research in pediatric endocrinology* 2013; **5**:236-239.
44. Griffin KJ, Thompson PA, Gottschalk M, Kyllo JH, Rabinovitch A. Combination therapy with sitagliptin and lansoprazole in patients with recent-onset type 1 diabetes (REPAIR-T1D): 12-month results of a multicentre, randomised, placebo-controlled, phase 2 trial. *The Lancet Diabetes & Endocrinology* 2014; **2**:710-718.
45. Hari Kumar KVS, Shaikh A, Prusty P. Addition of exenatide or sitagliptin to insulin in new onset type 1 diabetes: A randomized, open label study. *Diabetes Research and Clinical Practice* 2013; **100**:e55-e58.
46. C-Path. C-Path Virtual Workshop to Feature Latest Advances in Clinical Trials for T1D. 2021. https://c-path.org/c-path-virtual-workshop-to-feature-latest-advances-in-clinical-trials-for-t1d/. Accessed August 2021.
47. Skyler JS, Greenbaum CJ, Lachin JM, Leschek E, Rafkin-Mervis L, Savage P*, et al.* Type 1 Diabetes TrialNet--an international collaborative clinical trials network. *Ann N Y Acad Sci* 2008; **1150**:14-24.
48. National Institute for Health and Care Excellence. Type 1 diabetes in adults: diagnosis and management. *NICE guideline [NG17]*. [London]: NICE 2015. https://www.nice.org.uk/guidance/ng17. Accessed September 2020.
49. NCT02871089. Closed Loop From Onset in Type 1 Diabetes. https://ClinicalTrials.gov/show/NCT02871089.
50. NCT04233034. Hybrid Closed Loop Therapy and Verapamil for Beta Cell Preservation in New Onset Type 1 Diabetes. https://ClinicalTrials.gov/show/NCT04233034.

Tables

Study ID (No. articles, Age category)	Sample Size at randomisation (Intervention; comparator)	Baseline c-pep (nmol/L)	Intervention (Dose; frequency)	Comparator (Dose; Frequency)	Intervention/Comparator Duration	C-Peptide Measurement; Stimulant	Timepoints at which C-Peptide measurement reported	Time outcome reported (months)	Other outcomes of relevance measured
Alternative Insulin Preparations									
Asplin 1987 **(1, C)[a]**	112 (56;55)	Fasting intervention: 0.19 Control: 0.15	Pure porcine insulin (Daily)	Improved Single Peak mixed bovine/ porcine insulin (Daily)	12/12 months	Fasting; Stimulant not reported	NR	0, 1, 2, 4, 6, 9, 12	HbA1c; Glucose variability; Insulin Dose; Adverse Events
Marshall 1988 **(1, C)**	138 (68; 70)	Fasting intervention:0.17 control: 0.15	Human insulin (Once or twice daily)	Porcine insulin (Once or twice daily)	24/24 months	Fasting; Meal stimulated	0, 90 minutes	0, 3, 6, 9, 12, 15, 18, 21, 24	HbA1c; Insulin dose;
Recasens 2003 **(1, A)**	45 (22; 23)	Fasting intervention:0.27 Control: 0.27	Lispro Insulin (3-5 daily doses)	Regular insulin (3-5 daily doses)	12/12 months	Fasting; Glucagon stimulated	0, Max stimulated	0, 1, 4, 8, 12	HbA1c; Insulin dose; Hypoglycaemia; Weight
Bang 2011 **(1, C, AD)**	120 (41 Glargine and 39 Detemir; 40)	Fasting intervention: (median) prepubertal 0.3, pubertal 0.64	Glargine; Detemir (NR)	NPH insulin (NR)	12/12 months	Fasting; Meal stimulated	0, AUC (2hrs)	6, 12	HbA1c; Glucose variability; Insulin dose

		control: prepubertal 0.35, pubertal 0.41							
Continuous subcutaneous insulin infusion									
Flores d'Arcais 1984 **(1, C, AD)**	15 (9; 6)	Fasting intervention: 0.21 control: 0.17	Continuous subcutaneous insulin infusion (CSII) – pump (Dose adjusted; continuous)	Intensified conventional insulin treated injections (Dose adjusted; 3 times daily)	10/10 days	Fasting; Stimulant not reported	NR	0, 0.5, 1, 2, 3, 6, 9, 12	HbA1c; Insulin dose; Hypoglycaemia; Adverse events
Edelmann 1987 **(1, M)**	14 (7; 7)	Fasting intervention: 0.08 control: 0.08	Continuous subcutaneous insulin infusion (CSII) – pump (Dose adjusted; continuous)	Conventional insulin injections (Dose adjusted; 1-2 injections daily)	12/12 months	Fasting; Stimulant not reported	0 mins	0, 5, 6, 7, 12	HbA1c; Glucose variability; Insulin dose; Adverse events
De Beaufort 1989 **(1, M)**	30 (15; 15)	NR	Continuous subcutaneous insulin infusion (CSII) – pump (NR)	Conventional insulin injections (NR)	24/24 months	Fasting; Glucagon stimulated	0, peak stimulation (timepoint not clear)	6, 12, 18, 24	HbA1c; Insulin dose; Hypoglycaemia; Adverse events; Urinary C-peptide

Shah 1989 **(1, C, AD)**	26 (12; 14)	Max stim (60min) - intervention: 0.22 control: 0.19	Continuous subcutaneous insulin infusion (CSII) – pump (Programmed to maintain glucose levels between 3.3 and 4.4 mmol/L; Continuous)	Conventional insulin injections (Dose adjusted; 2 injections daily)	14 days / 12 months	Fasting; Meal stimulated	0, 60 minutes	0, 3, 6, 9 and 12	HbA1c; Insulin dose; Hypoglycaemia; Urinary C-peptide
Pozzilli 2003 **(1, M)**[b]	23 (7; 12)	Fasting, intervention: 0.21 control 0.25	Continuous subcutaneous insulin infusion (CSII) – pump (Dose adjusted; continuous)	Intensive subcutaneous insulin therapy (3 rapid + 1 intermediate injection (NPH); daily)	24/24 months	Fasting; Stimulant not reported	NR	0, 12, 24	HbA1c; Insulin dose; Hypoglycaemia
Thrailkill 2011 **(1, C, AD)**	24 (12; 12)	No baselines reported	Continuous subcutaneous insulin infusion (CSII) – pump (Dose adjusted; continuous)	Multiple daily insulin injections (Dose adjusted)	12/12 months	Fasting; Meal stimulated	0, 30, 60, 90, 120 mins; AUC 2hrs	6, 12	HbA1c; Insulin dose; Hypoglycaemia
Ekstrom 2014 **(2, C, AD)**[c]	72 (34; 38)	No baselines reported	Continuous subcutaneous insulin infusion (CSII) – pump (NR; continuous)	Multiple daily insulin injections (NR)	24/24 months	Fasting; Stimulant not reported	0 mins	6, 12, 24	HbA1c; Insulin dose
Lang 2017 **(1, C, AD)**[d]	79 (23; (MSII1 30, MSII2 26)	No baselines reported	Continuous subcutaneous insulin infusion (CSII) – pump (NR; continuous)	Multiple daily insulin injections (MSII1 and MSII2) (MSII1 one injection at bedtime; MSII2 2	6/6 months	Fasting; Meal stimulated	120 minutes	3, 6	HbA1c; Insulin dose; Hypoglycaemia;

				injections at bedtime and early morning)					
Intravenous Insulin Delivery									
Schnell 1997 **(1, M)**	19 (9; 10)	Fasting; intervention: 0.4 Control: 0.39	Continuous intravenous insulin infusion pump (Constant basal rate adjusted to achieve fasting euglycaemia)	Intensive SC insulin (Dose adjusted; 4 times daily)	2 weeks / 12 months	Fasting; Glucagon and Meal stimulated measurements	Glucagon 0, 6 mins Meal 0, 30, 60, 90, 120 mins; AUC 2hrs	Glucagon 0, 3, 7, 12 Meal 0, 5, 9, 12	HbA1c; Insulin dose; Hypoglycaemia; Urinary C-peptide
Perlman 1984 **(1, C, AD)**	14 (7; 7)	Fasting; intervention: 0.1 control: 0.11	Continuous intravenous insulin infusion pump (Constant basal rate adjusted to achieve fasting euglycaemia)	Conventional SC insulin (Dose adjusted; Daily)	Minumim 28 days of infusion / 12 months	Fasting; Meal stimulated	0, 90 mins (max stimulated)	0, 1, 4, 12	HbA1c; Insulin dose; Urinary C-peptide
Enander 2011 **(2, M)**	54 (28; 26)	Non fasting random: intervention: 0.34 control: 0.3	Continuous intravenous insulin infusion pump (Constant basal rate adjusted to achieve fasting euglycaemia)	Multiple daily insulin injections (MDI) (Age and plasma glucose level dependent; Daily)	48-72 hours / 24 months	Fasting and Non-fasting; Meal stimulated	0, 30, 90, 120 minutes; AUC 2hrs	0, 6, 12, 24	HbA1c; Insulin dose; Hypoglycaemia
Intensive Insulin Therapy									

Madsbad 1982 **(2, AD, A)**[e]	16 (7; 9)	Fasting, intervention: 0.08 control: 0.12 max stim 120min (meal), intervention: 0.18 control: 0.17	Fast-acting insulin for ten days and there after conventionally as for control group (9 injections; daily)	Conventional therapy: long-acting Lente or Monotard insulins (1-2 injections; daily)	10 days / 18 months	Fasting; Meal stimulated	-10, 0, 120 mins, AUC 3hrs	0, 6, 9, 12, 15, 18	Glucose variability; Insulin dose;
Linn 1996 **(1, A)**	49 (group allocation not reported)	Max stim 6min (glucagon) intervention: 0.39 control: 0.42	Intensive insulin therapy (At least 3 injections; daily)	Convetional insulin therapy including mixed intermediate and rapid-acting insulin (1-2 injections; daily)	60/60 months	Fasting; Glucagon stimulated	6 mins	0, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60	HbA1c; Insulin dose; Hypoglycaemia
NCT00564018 2007 **(Unpublished trial registry data)** **(1, C, AD)**[f]	33 (11 Detemir; 10 NPH; 12 Glargine)	NR	Three arm Group 1: Combination of insulins detemir and aspart Group 2: combination of insulins glargine and aspart Group 3: combination of insulins NPH and aspart	Three arm (see intervention)	Unclear	AUC; Meal stimulated	NR	6	HbA1c, Insulin dose; Adverse events

The DCCT Research Group 1998 **(1, A)**[g]	303 (138; 165)	Max stim 90min (meal) intervention: median 0.33 control: 0.32	Intensive insulin therapy (3-4 injections; daily or continuous subcutaneous infusion of insulin)	Conventional insulin therapy (1-2 injections; daily)	72/72 months	Fasting; Meal stimulated	90 mins	0, 12, 24, 36, 48, 60, 72	HbA1c; Hypoglycaemia
Wang 2017 **(2, C, AD)**	60 (20 group 1, 20 group 2; 20)	Fasting (high dose group): 0.2 control: 0.22	Group 1 - High dose continuous subcutaneous insulin infusion Group 2 - Medium dose continuous subcutaneous insulin infusion (Dose adjusted; continuous)	Low dose continuous subcutaneous insulin infusion (Dose adjusted; continuous)	3/3 weeks	Fasting; Stimulant not reported	0 minutes	0, 1, 3, 6, 12	HbA1c; Glucose variability; Insulin dose; Hypoglycaemia; Ketoacidosis;
Additional use of Glucose Sensing									
Kordonouri 2010 **(4, C, AD)**[h]	160 (80; 80)	Fasting intervention: 0.16 control: 0.15	Sensor Augmented Pump Therapy (REAL-Time Insulin Pump and Continuous Glucose Monitoring System) (Dose adjusted; continuous)	Insulin Pump Alone (Dose adjusted; continuous)	24/24 months	Fasting; Stimulant not reported	0 minutes	0, 12, 24	HbA1c; Glucose variability; Insulin dose; Hypoglycaemia; Ketoacidosis; Quality of Life

Buckingham 2013 **(2, M)**[i]	68 (48; 20)	2HR AUC intervention: 0.29 control: 0.35	Intensive insulin therapy (hybrid closed-loop control (HCLC) followed by home use of Sensor Augmented Pump therapy (Dose adjusted; continuous)	Standard diabetes management as practiced at the participating diabetes treatment centers (NR)	12/12 months	Fasting; Meal Stimulated	AUC 2hrs	0, 3, 6, 9, 12	HbA1c; Glucose variability; Insulin dose; Hypoglycaemia; Adverse events
Adjunctive Therapies									
Sanders 1990 **(1, C, AD)**[j]	26 (13; 11)	No baselines reported	Tolazamide (sulfonylurea) (10mg/kg; once daily)	Placebo (Once daily)	15/15 months	Fasting; Glucose stimulated	0, 60 minutes	5, 9, 11	HbA1c; Glucose variability; Insulin dose; Adverse events
Selam 1993 **(1, A)**[k]	27 (13; 14)	Fasting, intervention: 0.21 control: 0.19 Max stim (6min) glucagon, intervention: 0.35 control: 0.3	Glipizide (sulphonylurea) (Glipizide dose dependent upon insulin dose; once daily)	Regular insulin therapy (NPH) (Dose adjusted; 2-4 injections daily)	24/24 weeks (but not clearly reported in the paper)	Fasting; Glucagon stimulated	0, 6 minutes	0, 1, 2, 6	Hypoglycaemia;Ketoacidosis

Fallucca 1996 **(1, NR)**	22 (11; 11)	Fasting, intervention: 0.31 control: 0.29 Max stim (60min) meal, intervention: 0.5 control: 0.51	Gliclazide (80mg; twice daily)	Placebo (NR)	18/18 months	Fasting; Meal stimulated	0, 60 minutes	0, 6, 12, 18	HbA1c; Glucose variability; Insulin dose; Weight
Tafuri 2013 **(1, C, AD)**	15 (8; 7)	Peak 0-120min (meal) intervention: 0.5 control: 0.5	Pioglitazone (15 mg/day for children 6-10 years, 30 mg/day for children 10-15 years and 45 mg/day for children >15 years)	Placebo (NR)	5.5/5.5 months	Fasting; Boost stimulated	Peak	0, 5.5	HbA1c; Adverse events
Harri Kumar 2013 **(2, A)**[L]	18 (6 group 1, 6 group 2; 6)	Max stim 120min (meal) intervention: 0.13 control: 0.13	Group 1 - Exenatide (DPP4 inhibitor) Group 2 - Sitagliptin (GLP analogues) (Group 1 - 5 microgram (one month) and 10 microgram (from second month onward); twice daily Group 2 - 100mg; once daily)	Standard insulin regime (2 injections; daily (later increased to 3 injections; daily if required))	12/12 months	Fasting; Meal stimulated	120 minutes	0, 12	HbA1c; Insulin dose; Hypoglycaemia; Ketoacidosis; Adverse events; Weight

Griffin 2014 **(1, AD, A)**[m]	70 (46; 22)	2HR AUC intervention: 0.66 control: 0.75	Combination of Sitagliptin (DPP4 inhibitor) and lansoprazole (PPI) (≥18 100mg sitagliptin, 60mg lansoprazole <18 50mg sitagliptin, 30mg lansoprazole; once daily)	Placebo (Once daily)	12/12 months	Fasting; Meal stimulated	AUC 2hrs	0, 6, 12	HbA1c; Glucose variability; Insulin dose; Hypoglycaemia; Adverse events; Compliance

Abbreviations: *HbA1c=haemoglobin A1c; Age categories: C=children; AD=adolescents, A=adults, M=mixed; NR=not reported; NPH=neutral protamine hagedorn; IV=intravenous; SC=sub-cutaneous; AUC=area under the curve; DPP4=dipeptidyl peptidase-4; GLP1=glucagon-like peptide-1; PPI=proton pump inhibitor.*

[a]Baseline table numbers do not add up to 112. [b]4 patients dropped out before treatment. Both groups were also on nicotinamide 25mg/kg/day. [c]Data from abstract and thesis. C-peptide data unavailable. [d]Controls: MSII1 (the patients were given insulin aspart before meals followed by one-time injection of insulin detemir at bedtime), MSII2 (the patients were given insulin aspart before meals followed by two-time injection of insulin detemir respectively at bedtime and in the early morning). [e]Data from 6 month and 18 month follow up papers. [f]Data only available from clinical trial registry, no publications. Study terminate early but little detail given. [g]303 are a subgroup of responders taken from a larger trial. [h]Data from 12 month and 24 month follow up papers. [i]71 enrolled but only antibody positive patients included. [j]2 patients withdrew during the first month. [k]Gliplizide started after 1 month of intensive insulin therapy. If insulin dose <20 u/day: d/c insulin, start Glipizide 10-40 mg/day. If insulin >20 u/day: start Glipizide 10-40 mg/day and taper insulin by 50% weekly if glucose < 140 mg/dl continue until complete discontinuation of insulin. [L]Two intervention groups which cross different subgroups. [m]Unclear if some patients were lost before baseline measurements

Table 1. Glucose Control Table of Study Characteristics

Study ID	Random sequence generation	Allocation concealment	Blinding of patients	Blinding of C-peptide outcome	Incomplete outcome data C-peptide outcome	Selective reporting (e.g. only certain outcomes, no adverse events).
Alternative Insulin Preparations						
Asplin 1987	U	U	L	U	U	U
Marshall 1988	U	U	L	L	H	H
Recasens 2003	U	U	N/A	U	L	U
Bang 2011	U	U	U	U	L/U	U
Continuous Subcutaneous Insulin Infusion						
Flores D'Arcasis 1984	U	U	U	U	L	U
Edelmann 1987	U	U	U	U	L	U
De Beaufort 1989	U	U	N/A	U	L	U
Shah 1989	L	U	H	L	L	L
Pozzilli 2003	L	U	U	U	U	L
Thrailkill 2011	U	U	U	U	U	L
Lang 2017	U	U	U	U	H	H
Ekstrom 2014	U	U	N/A	U	U	U

Intravenous Insulin Therapy						
Schnell 1997	U	U	N/A	U	L	U
Enander 2018	L	U	N/A	U	H	U
Perlman 1984	U	U	N/A	U	L	U
Intensive Insulin Therapy						
Madsbad 1982	U	U	N/A	U	U	U
DCCT 1998	U	U	U	L	L	L
Linn 1996	L	U	U	U	H	U
Wang 2017	L	L	N/A	L	L	U
NCT00564018 2007[a]	U	U	U	U	U	U
Additional use of Glucose Sensing						
Kordonouri 2010	L	L	N/A	L	L	U
Buckingham 2013	U	U	N/A	L	U	U
Adjunctive Therapies						
Sanders 1990	L	U	U	U	U	L
Selam 1993	L	U	H	H	L	U
Fallucca 1996	U	U	U	U	L	U
Tafuri 2013	U	U	U	U	U	L

Harri Kumar 2013	U	U	H	H	L	L
Griffin 2014	L	L	L	H	L	L

NB - in this table the best RoB results have been taken from studies with multiple publications (the one with the most information to address each criteria)

N/A = Not applicable as blinding was not possible during the study.

[a]*Information is based only from the clinicaltrials.gov register and no publications are available for this study*

Table 2. Glucose Control - Risk of Bias of Included Studies

Figure Legend

Figure 1. Image illustrating alternative methods of measuring C-Peptide

Figure 2. PRISMA flow diagram of studies included in the review and the Glucose Group from both the original and updated searches

Figure 3. Summary plots of meta-analyses findings for each intervention subgroup for each primary outcome at each follow-up time point. (A) HbA1c, (B) Insulin dose, (C) C-peptide, (D) C-peptide AUC. Each analysis is cross referenced to the corresponding Forest plot in Supplementary Figures from which the data was obtained. Brackets = number of studies contributing to each analysis.