Pediatr Diabetes. 2016 Nov;17(7):469-477. doi: 10.1111/pedi.12424. Epub 2016 Aug 3.

Modulation of type 1 and type 2 diabetes risk by the intestinal microbiome.

Paun A[1,2], Danska JS[3,4,5].

Abstract

The prevalence of type 1 and type 2 diabetes have both risen dramatically over the last 50 years. Recent findings point towards the gut microbiota as a potential contributor to these trends. The hundred trillion bacteria residing in the mammalian gut have established a symbiotic relation with their host and influence many aspects of host metabolism, physiology, and immunity. In this review, we examine recent data linking gut microbiome composition and function to anti-pancreatic immunity, insulin-resistance, and obesity. Studies in rodents and human longitudinal studies suggest that an altered gut microbiome characterized by lower diversity and resilience is associated with type 1 and type 2 diabetes. Through its metabolites and enzymatic arsenal, the microbiota shape host metabolism, energy extracted from the diet and contribute to the normal development of the immune system and to tissue inflammation. Increasing evidence underscores the importance of the maternal microbiome, the gestational environment and the conditions of newborn delivery in establishing the gut microbiota of the offspring. Perturbations of the maternal microbiome during gestation, or that of the offspring during early infant development may promote a pro-inflammatory environment conducive to the development of autoimmunity and metabolic disturbance. Collectively the findings reviewed herein underscore the need for mechanistic investigations in rodent models and in human studies to better define the relationships between microbial and host inflammatory activity in diabetes, and to evaluate the potential of microbe-derived therapeutics in the prevention and treatment of both forms of diabetes.J Diabetes Res. 2016;2016:3271293. doi: 10.1155/2016/3271293. Epub 2015 Dec 10.

REVIEW A R T I C L E

Modulation of type 1 and type 2 diabetes risk by the intestinal microbiome

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The prevalence of type 1 and type 2 diabetes have both risen dramatically over the last 50 years. Recent findings point towards the gut microbiota as a potential contributor to these trends. The hundred trillion bacteria residing in the mammalian gut have established a symbiotic relation with their host and influence many aspects of host metabolism, physiology,

and immunity. In this review, we examine recent data linking gut microbiome composition and function to anti-pancreatic immunity, insulin-resistance, and obesity. Studies in rodents and human longitudinal studies suggest that an altered gut microbiome characterized by lower diversity and resilience is associated with type 1 and type 2 diabetes. Through its metabolites and enzymatic arsenal, the microbiota shape host metabolism, energy extracted from the diet and contribute to the normal development of the immune system and to tissue inflammation. Increasing evidence underscores the importance of the maternal microbiome, the gestational environment and the conditions of newborn delivery in establishing the gut microbiota of the offspring. Perturbations of the maternal microbiome during gestation, or that of the offspring during early infant development may promote a pro-inflammatory environment conducive to the development of autoimmunity and metabolic disturbance. Collectively the findings reviewed herein underscore the need for mechanistic investigations in rodent models and in human studies to better define the relationships between microbial and host inflammatory activity in diabetes, and to evaluate the potential of microbe-derived therapeutics in the prevention and treatment of both forms of diabetes.

KEYWORDS

gut microbiome, type 1 diabetes, type 2 diabetes

Effect of Vitamins C and E on Endothelial Function in Type 1 Diabetes Mellitus.

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BACKGROUND/OBJECTIVES:
Endothelial dysfunction due to hyperglycemia-induced oxidative damage is an important predictor of future cardiovascular risk in patients with type 1 diabetes mellitus (T1DM) and is present in adolescent T1DM. We hypothesized that combined treatment with the antioxidant vitamins C and E might improve endothelial function (EF) and other biochemical risk factors in adolescents with T1DM.

SUBJECTS/METHODS:
Open-label antioxidant supplementation was given for six weeks with endpoint measurements collected at baseline and study completion. Endpoints measured included EF and plasma measurements of biochemical endothelial risk.

RESULTS:
Two males and 7 females were studied. Mean age was 12.9 ± 0.9 yrs; mean T1DM duration was 5.5 ± 2.5 yrs; mean BMI was 22.1 ± 3.8 kg/m(2); and mean hemoglobin A1c was 9.3 ± 1.1%. No differences were found for EF, high sensitivity CRP, total antioxidant capacity, adiponectin, or endothelial progenitor cells (EPCs) between before and after combined vitamin C and E therapy.

CONCLUSIONS:
Our negative study results do not support previous findings of decreased oxidative damage, improved endothelial function, and increased vascular repair capacity with antioxidant therapy. Longer term studies may be needed to determine the effects, if any, of combined antioxidant therapy on EPCs, EF, and markers of micro- and macrovascular complications in T1DM.

Diabetes Care. 2016 Feb;39(2):264-70. doi: 10.2337/dc15-1498. Epub 2015 Dec 17.

Intranasal Glucagon for Treatment of Insulin-Induced Hypoglycemia in Adults With Type 1 Diabetes: A Randomized Crossover Noninferiority Study.

Rickels MR[1], Ruedy KJ[2], Foster NC[3], Piché CA[4], Dulude H[4], Sherr JL[5], Tamborlane WV[5], Bethin KE[6], DiMeglio LA[7], Wadwa RP[8], Ahmann AJ[9], Haller MJ[10], Nathan BM[11], Marcovina SM[12], Rampakakis E[13], Meng L[13], Beck RW[2]; T1D Exchange Intranasal Glucagon Investigators.

OBJECTIVE:

Treatment of severe hypoglycemia with loss of consciousness or seizure outside of the hospital setting is presently limited to intramuscular glucagon requiring reconstitution immediately prior to injection, a process prone to error or omission. A needle-free intranasal glucagon preparation was compared with intramuscular glucagon for treatment of insulin-induced hypoglycemia.

RESEARCH DESIGN AND METHODS:

At eight clinical centers, a randomized crossover noninferiority trial was conducted involving 75 adults with type 1 diabetes (mean age, 33 ± 12 years; median diabetes duration, 18 years) to compare intranasal (3 mg) versus intramuscular (1 mg) glucagon for treatment of hypoglycemia induced by intravenous insulin. Success was defined as an increase in plasma glucose to ≥70 mg/dL or ≥20 mg/dL from the glucose nadir within 30 min after receiving glucagon.

RESULTS:

Mean plasma glucose at time of glucagon administration was 48 ± 8 and 49 ± 8 mg/dL at the intranasal and intramuscular visits, respectively. Success criteria were met at all but one intranasal visit and at all intramuscular visits (98.7% vs. 100%; difference 1.3%, upper end of 1-sided 97.5% CI 4.0%). Mean time to success was 16 min for intranasal and 13 min for intramuscular ($P < 0.001$). Head/facial discomfort was reported during 25% of intranasal and 9% of intramuscular dosing visits; nausea (with or without vomiting) occurred with 35% and 38% of visits, respectively.

CONCLUSIONS:

Intranasal glucagon was highly effective in treating insulin-induced hypoglycemia in adults with type 1 diabetes. Although the trial was conducted in a controlled setting, the results are applicable to real-world management of severe hypoglycemia, which occurs owing to excessive therapeutic insulin relative to the impaired or absent endogenous glucagon response.

JAMA Ophthalmol. 2016 Feb;134(2):137-45. doi: 10.1001/jamaophthalmol.2015.4606.

Effects of Prior Intensive Insulin Therapy and Risk Factors on Patient-Reported Visual Function Outcomes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Cohort.

Writing Team for the DCCT/EDIC Research Group, Gubitosi-Klug RA[1], Sun W[2], Cleary PA[2], Braffett BH[2], Aiello LP[3], Das A[4], Tamborlane W[5], Klein R[6].

IMPORTANCE:
Preservation of vision in patients with diabetes mellitus is critical. Interventions to improve glycemic control through early intensive treatment of diabetes reduce rates of severe retinopathy and preserve visual acuity.

OBJECTIVE:
To assess the effects of prior intensive insulin treatment and risk factors on patient-reported visual function in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort.

DESIGN, SETTING, AND PARTICIPANTS:
Cohort study of 1184 participants with type 1 diabetes from the DCCT/EDIC study (randomized clinical trial followed by an observational follow-up study) who completed the 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) during EDIC years 17 through 20 (September 1, 2009, through April 30, 2014) in 28 institutions across the United States and Canada.

MAIN OUTCOMES AND MEASURES:
The primary outcome was the composite NEI-VFQ-25 score. Secondary outcomes were visual acuity (measured by the Early Treatment Diabetic Retinopathy Study protocol), retinopathy level (determined by masked grading of stereoscopic color fundus photographs), and NEI-VFQ-25 subscale scores. The composite NEI-VFQ-25 scale and its subscales were scored 0 to 100, corresponding to poor to excellent function, respectively.

RESULTS:
The overall average NEI-VFQ-25 score for 1184 DCCT/EDIC participants (mean [SD] age, 52.3 [6.9] years; 48% female) with a 30-year duration of diabetes was high (all participants: median, 91.7; interquartile range [IQR], 89.7-96.9; intensive treatment [n = 605]: median, 94.7; IQR, 91.0-97.2; conventional treatment [n = 579]: median, 94.0; IQR, 88.4-96.1; P = .006 for intensive vs conventional). After adjustment for sex, age, hemoglobin A1c level, and retinopathy level at DCCT baseline, the former intensive treatment group had a significant,

albeit modest, improvement in overall NEI-VFQ-25 score compared with the former conventional diabetes treatment group (median difference, -1.0; 95% CI, -1.7 to -0.3; P = .006). This beneficial treatment effect was fully attributed to the prior glycemic control in DCCT (explained treatment effect: 100%). Those with visual acuity worse than 20/100 reported the largest decline in visual function (median difference, -21.0; 95% CI, -40.5 to -1.6; P = .03).

CONCLUSIONS AND RELEVANCE:
In the DCCT/EDIC cohort, patient-reported visual function remains high in both treatment groups, comparable to previous reports of overall health-related quality of life. Intensive diabetes therapy modestly improved NEI-VFQ-25 score 30 years after the start of the DCCT, the benefit underestimated owing to more nonparticipants from the conventional treatment group. Visual acuity had the greatest effect on patient-reported visual function from among all risk factors.

J Clin Endocrinol Metab. 2016 Mar;101(3):928-36. doi: 10.1210/jc.2015-3882. Epub 2016 Jan 12.

Bone Structure and Predictors of Fracture in Type 1 and Type 2 Diabetes.

Starup-Linde J[1], Lykkeboe S[1], Gregersen S[1], Hauge EM[1], Langdahl BL[1], Handberg A[1], Vestergaard P[1].

CONTEXT:

Type 1 and type 2 diabetes mellitus are associated with an increased risk of fracture.

OBJECTIVE:

The objective of the study was to compare the bone structure and density between type 1 and type 2 diabetes patients and to investigate fracture associations.

DESIGN:

This was a cross-sectional study.

SETTING AND PATIENTS:

Physician-diagnosed type 1 and type 2 diabetes patients were included from the outpatient clinics at two university hospitals participated in the study.

MAIN OUTCOME MEASURES:

Bone density and structure were assessed by dual-energy x-ray absorptiometry and high-resolution peripheral quantitative computed tomography. Blood samples were collected for bone turnover markers. Prevalent vertebral fractures were assessed by vertebral fracture assessment and x-ray, and incident fractures were collected from The Danish National Hospital Discharge Register.

RESULTS:

Bone mineral density (BMD) was higher in type 2 than type 1 diabetes patients at the hip, femur, and spine; however, only the hip differed in multivariate-adjusted models. Bone tissue stiffness at the tibia was increased in type 2 diabetes patients also in adjusted models. Sclerostin levels were inversely associated with fracture in type 1 diabetes patients. The patients with the highest tertile of sclerostin had an 81% decreased risk of a fracture compared with the lowest tertile.

CONCLUSIONS:

Type 1 and type 2 diabetes patients differ in BMD of the hip and tissue stiffness at the tibia. Sclerostin may be a marker independent of BMD to predict fractures in type 1 diabetes patients and thus potentially of clinical importance. Studies with longer follow-up are needed.

BMJ Open. 2016 Dec 5;6(12):e012307. doi: 10.1136/bmjopen-2016-012307.

Nocturnal antihypertensive treatment in patients with type 1 diabetes with autonomic neuropathy and non-dipping: a randomised, placebo-controlled, double-blind cross-over trial.

Hjortkjær HØ[1], Jensen T[1], Kofoed KF[2,3], Mogensen UM[2], Sigvardsen PE[2], Køber L[2], Hilsted KL[1], Corinth H[1], Theilade S[4], Hilsted J[1].

OBJECTIVES:

Cardiovascular autonomic neuropathy (CAN) and abnormal circadian blood pressure (BP) rhythm are independent cardiovascular risk factors in patients with diabetes and associations between CAN, non-dipping of nocturnal BP and coronary artery disease have been demonstrated. We aimed to test if bedtime dosing (BD) versus morning dosing (MD) of the ACE inhibitor enalapril would affect the 24-hour BP profile in patients with type 1 diabetes (T1D), CAN and non-dipping.

SETTING:

Secondary healthcare unit in Copenhagen, Denmark.

PARTICIPANTS:

24 normoalbuminuric patients with T1D with CAN and non-dipping were included, consisting of mixed gender and Caucasian origin. Mean±SD age, glycosylated haemoglobin and diabetes duration were 60±7 years, 7.9±0.7% (62±7 mmol/mol) and 36±11 years.

INTERVENTIONS:

In this randomised, placebo-controlled, double-blind cross-over study, the patients were treated for 12 weeks with either MD (20 mg enalapril in the morning and placebo at bedtime) or BD (placebo in the morning and 20 mg enalapril at bedtime), followed by 12 weeks of switched treatment regimen.

PRIMARY AND SECONDARY OUTCOME MEASURES:

Primary outcome was altered dipping of nocturnal BP. Secondary outcomes included a measurable effect on other cardiovascular risk factors than BP, including left ventricular function (LVF).

RESULTS:

Systolic BP dipping increased 2.4% (0.03-4.9%; p=0.048) with BD compared to MD of enalapril. There was no increase in mean arterial pressure dipping (2.2% (-0.1% to 4.5%; p=0.07)). No difference was found on measures of LVF (p≥0.15). No adverse events were registered during the study.

CONCLUSIONS:

We demonstrated that patients with T1D with CAN and non-dipping can be treated with an ACE inhibitor at night as BD as opposed to MD increased BP dipping, thereby diminishing the abnormal BP profile. The potentially beneficial effect on long-term cardiovascular risk remains to be determined.

Int J Endocrinol. 2016;2016:8350158. Epub 2016 Oct 13.

No Contribution of GAD-65 and IA-2 Autoantibodies around Time of Diagnosis to the Increasing Incidence of Juvenile Type 1 Diabetes: A 9-Year Nationwide Danish Study.

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Abstract

Aims. A new perspective on autoantibodies as pivotal players in the pathogenesis of type 1 diabetes (T1D) has recently emerged. Our key objective was to examine whether increased levels of autoantibodies against the *β*-cell autoantigens glutamic acid decarboxylase (isoform 65) (GADA) and insulinoma associated antigen-2A (IA-2A) mirrored the 3.4% annual increase in incidence of T1D. *Methods.* From the Danish Childhood Diabetes Register, we randomly selected 500 patients and 500 siblings for GADA and IA-2A analysis (1997 through 2005). Blood samples were taken within three months after onset. A robust log-normal regression model was used. Nine hundred children and adolescents had complete records and were included in the analysis. Cochran-Armitage test for trend was used to evaluate changes in prevalence of autoantibody positivity by period. *Results.* No significant changes in levels of GADA and IA-2A were found over our 9-year study period. No trends in autoantibody positivity-in either patients or siblings-were found. Levels of GADA and IA-2A were significantly associated with HLA risk groups and GADA with age. *Conclusion.* The prevalence of positivity and the levels of GADA and IA-2A have not changed between 1997 and 2005 in newly diagnosed patients with T1D and their siblings without T1D.

N Engl J Med. 2016 Aug 18;375(7):644-54. doi: 10.1056/NEJMoa1602494.

Closed-Loop Insulin Delivery during Pregnancy in Women with Type 1 Diabetes.

Stewart ZA[1], Wilinska ME[1], Hartnell S[1], Temple RC[1], Rayman G[1], Stanley KP[1], Simmons D[1], Law GR[1], Scott EM[1], Hovorka R[1], Murphy HR[1].

BACKGROUND:
In patients with type 1 diabetes who are not pregnant, closed-loop (automated) insulin delivery can provide better glycemic control than sensor-augmented pump therapy, but data are lacking on the efficacy, safety, and feasibility of closed-loop therapy during pregnancy.
METHODS:
We performed an open-label, randomized, crossover study comparing overnight closed-loop therapy with sensor-augmented pump therapy, followed by a continuation phase in which the closed-loop system was used day and night. Sixteen pregnant women with type 1 diabetes completed 4 weeks of closed-loop pump therapy (intervention) and sensor-augmented pump therapy (control) in random order. During the continuation phase, 14 of the participants used the closed-loop system day and night until delivery. The primary outcome was the percentage of time that overnight glucose levels were within the target range (63 to 140 mg per deciliter [3.5 to 7.8 mmol per liter]).
RESULTS:
The percentage of time that overnight glucose levels were in the target range was higher during closed-loop therapy than during control therapy (74.7% vs. 59.5%; absolute difference, 15.2 percentage points; 95% confidence interval, 6.1 to 24.2; P=0.002). The overnight mean glucose level was lower during closed-loop therapy than during control therapy (119 vs. 133 mg per deciliter [6.6 vs. 7.4 mmol per liter], P=0.009). There were no significant differences between closed-loop and control therapy in the percentage of time in which glucose levels were below the target range (1.3% and 1.9%, respectively; P=0.28), in insulin doses, or in adverse-event rates. During the continuation phase (up to 14.6 additional weeks, including antenatal hospitalizations, labor, and delivery), glucose levels were in the target range 68.7% of the time; the mean glucose level was 126 mg per deciliter (7.0 mmol per liter). No episodes of severe hypoglycemia requiring third-party assistance occurred during either phase.
CONCLUSIONS:
Overnight closed-loop therapy resulted in better glucose control than sensor-augmented pump therapy in pregnant women with type 1 diabetes. Women receiving day-and-night closed-loop therapy maintained glycemic control during a high proportion of the time in a period that encompassed antenatal hospital admission, labor, and delivery. (Funded by the National Institute for Health Research and others; Current Controlled Trials number, ISRCTN71510001.)

Diabetes Care 2016;39:1151–1160 | DOI: 10.2337/dc16-0008

Day-and-Night Closed-Loop Glucose Control in Patients With Type 1 Diabetes Under Free-Living Conditions: Results of a Single-Arm 1-Month Experience Compared With a Previously Reported Feasibility Study of Evening and Night at Home

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OBJECTIVE

After testing of a wearable artificial pancreas (AP) during evening and night (E/N-AP) under free-living conditions in patients with type 1 diabetes (T1D), we investigated AP during day and night (D/N-AP) for 1 month.

RESEARCH DESIGN AND METHODS

Twenty adult patients with T1D who completed a previous randomized crossover study comparing 2-month E/N-AP versus 2-month sensor augmented pump (SAP) volunteered for 1-month D/N-AP nonrandomized extension. AP was executed by a model predictive control algorithm run by a modified smartphone wirelessly connected to a continuous glucose monitor (CGM) and insulin pump. CGM data were analyzed by intention-to-treat with percentage time-in-target (3.9– 10 mmol/L) over 24 h as the primary end point.

RESULTS

Time-in-target (mean 6 SD, %) was similar over 24 h with D/N-AP versus E/N-AP: 64.767.6 vs. 63.669.9 (P = 0.79), and bothwere higher than with SAP: 59.769.6 (P = 0.01 and P = 0.06, respectively). Time below 3.9 mmol/L was similarly and significantly reduced by D/N-AP and

E/N-AP versus SAP (both P < 0.001). SD of blood glucose concentration (mmol/L) was lower with D/N-AP versus E/N-AP during whole daytime: 3.2 6 0.6 vs. 3.4 6 0.7 (P = 0.003), morning: 2.7 6 0.5 vs. 3.1 6 0.5 (P = 0.02), and afternoon: 3.3 6 0.6 vs. 3.5 6 0.8 (P = 0.07), and was lower with D/N-AP versus SAP over 24 h: 3.160.5 vs. 3.360.6 (P = 0.049). Insulin delivery (IU) over 24 h was higher with D/N-AP and SAP than with E/N-AP: 40.6 6 15.5 and 42.3 6 15.5 vs. 36.6 6 11.6 (P = 0.03 and P = 0.0004, respectively).

CONCLUSIONS

D/N-AP and E/N-AP both achieved better glucose control than SAP under freeliving conditions. Although time in the different glycemic ranges was similar between D/N-AP and E/N-AP, D/N-AP further reduces glucose variability.

See accompanying articles, pp. 1123, 1127, 1135, 1143, 1161, 1168, 1175, and 1180.

High Sclerostin and Dickkopf-1 (DKK-1) serum levels in children and adolescents with type 1 diabetes mellitus.

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CONTEXT:
Childhood type 1 diabetes (T1DM) is associated with decreased bone mass. Sclerostin and dickkopf-1 (DKK-1) are Wnt inhibitors which regulate bone formation.
OBJECTIVE:
To evaluate sclerostin and DKK-1 levels in TD1M children and to analyze the influence of the glycaemic control on bone health.
DESIGN AND SETTING:
Cross-sectional study conducted at a clinical research center. Partecipants: One hundred and six T1DM subjects (12.2 ± 4 years), 66 on multiple daily injections (MDI) and 40 on continuous subcutaneous infusion of insulin (CSII), and 80 controls.
RESULTS:
The average of bone transmission time (BTT) and amplitude-dependent speed of sound (Ad-Sos) Z-scores was lower in diabetics than controls. Significant increased DKK-1 (3593 ± 1172 vs 2652 ± 689 pg/ml, $p<0.006$) and sclerostin (29.45 ± 12.32 vs 22.53 ± 8.29, $p<0.001$) levels were found in diabetics respect to controls, particularly in patients on MDI than ones on CSII. Glycaemic control was improved in CSII patients compared to MDI ones ($p<0.001$) and was also associated to a significant higher BMI-SDS ($p<0.002$) and BTT-Z-score ($p<0.02$). With adjustment for age multiple linear regression analysis for DKK-1 and sclerostin as dependent variables showed that levels of HbA1c%, glucose, 25(OH)-Vitamin D, osteocalcin, PTH, years of diabetes, BMI-SDS and AD-SoS-Z-score are the most important predictors ($p<0.0001$).
CONCLUSIONS:
Our study highlighted: 1. the high serum levels of DKK-1 and sclerostin in T1DM children, and their relationship with the altered glycaemic control; 2. the effect of CSII on the improvement of glycaemic control and bone health in T1DM children.

J Clin Endocrinol Metab. 2016 May;101(5):2141-8. doi: 10.1210/jc.2015-2776. Epub 2016 Feb 9.

Long-Term Insulin Independence in Type 1 Diabetes Mellitus Using a Simplified Autologous Stem Cell Transplant.

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CONTEXT:
Efforts to find a cure for type 1 diabetes have focused on the removal of the autoimmune pathophysiologic substrate, with the use of immunosuppressive regimens including autologous hematopoietic stem cell transplantation (AHSCT).

OBJECTIVE:
The main objective of determining long-term insulin independence as well as changes in glycated hemoglobin (HbA1c). Secondary outcomes were procedure morbidity and the need for hospital management.

DESIGN:
We enrolled patients with type 1 diabetes between 2012 and 2014. Median follow-up was 34 months (range, 25-56 mo).

SETTING:
Ambulatory care.

INTERVENTIONS:
We decided to carry out an AHSCT protocol using a less toxic and affordable simplified method based on fludarabine in an outpatient setting.

PATIENTS:
Patients were of both sexes, age 8-25 years, with positive levels of anti-GAD antibodies, a C-peptide level >1.0 ng/mL, and <3 months since diagnosis.

MAIN OUTCOME MEASURE(S):
Insulin independence.

RESULTS:
Sixteen patients were included. Overall response was 81% with seven patients achieving insulin independence (44%); six were partial responders (37%) whereas three were nonresponders (19%). The HbA1c level showed a mean decrease of -2.3% at 6 months in the Insulin Independence group. Median age was 12 years old (range, 8-17 years old). A mean of 11.5 × 10(6) CD34+ cells (SD ± 8.2) was obtained. Related mortality at 100 days was 0% as well as during follow-up. Outpatient setting was 100%.

CONCLUSIONS:
Simplified AHSCT in an outpatient setting is a feasible, safe and potentially therapeutic intervention for early-onset type 1 diabetes.

J Clin Endocrinol Metab. 2016 Sep;101(9):3506-15. doi: 10.1210/jc.2016-1451. Epub 2016 Aug 4.

Dapagliflozin as Additional Treatment to Liraglutide and Insuli n in Patients With Type 1 Diabetes.

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[1] Division of Endocrinology, Diabetes, and Metabolism, State University of New York at Buffalo, Buffalo, New York 14215.

CONTEXT:
It is imperative that novel approaches to treatment of type 1 diabetes (T1D) are devised.
OBJECTIVE:
The objective of the study was to investigate whether addition
of dapagliflozin to insulin and liraglutide results in a significant reduction in glycemia and body weight.
DESIGN:
This was a randomized clinical trial.
SETTING:
The study was conducted at a single academic medical center.
PARTICIPANTS:
Participants included T1D patients on liraglutide therapy for at least last 6 months.
INTERVENTION:
Thirty T1D patients were randomized (in 2:1 ratio) to receive either dapagliflozin 10 mg or placebo daily for 12 weeks.
MAIN OUTCOME MEASURE:
Change in mean glycated hemoglobin after 12 weeks of dapagliflozin when compared with placebo was measured.
RESULTS:
In the dapagliflozin group, glycated hemoglobin fell by 0.66% ± 0.08% from 7.8% ± 0.21% ($P < .01$ vs placebo), whereas it did not change significantly in the placebo group from 7.40% ± 0.20% to 7.30% ± 0.20%. The body weight fell by1.9 ± 0.54kg ($P < .05$ vs placebo). There was no additional hypoglycemia (blood glucose < 3.88 mmol/L; $P = .52$ vs placebo). In
the dapagliflozin group, there were significant increases in the plasma concentrations of glucagon by 35% ± 13% ($P < .05$), hormone-sensitive lipase by 29% ± 11% ($P < .05$), free fatty acids by 74% ± 32% ($P < .05$), acetoacetate by 67% ± 34% ($P < .05$), and β-hydroxybutyrate by 254% ± 81% ($P < .05$). Urinary ketone levels also increased significantly ($P < .05$). None of these changes was observed in the placebo group. Two patients in the dapagliflozin group developed diabetic ketoacidosis.

CONCLUSIONS:

Addition of dapagliflozin to insulin and liraglutide in patients with T1D results in a significant improvement in glycemia and weight loss while increasing ketosis. If it is decided to use this approach, then it must be used only by a knowledgeable patient along with an endocrinologist who is well versed with it

Diabetes Care. 2016 Apr;39(4):603-10. doi: 10.2337/dc15-1426. Epub 2015 Dec 17.

Risk Factors Associated With Severe Hypoglycemia in OlderAdults With Type 1 Diabetes.

Weinstock RS[1], DuBose SN[2], Bergenstal RM[3], Chaytor NS[4], Peterson C[4], Olson BA[3], Munshi MN[5], Perrin AJ[2], Miller KM[6], Beck RW[2], Liljenquist DR[7], Aleppo G[8], Buse JB[9], Kruger D[10], Bhargava A[11], Goland RS[12], Edelen RC[13], Pratley RE[14], Peters AL[15], Rodriguez H[16], Ahmann AJ[17], Lock JP[18], Garg SK[19], Rickels MR[20], Hirsch IB[4]; T1D Exchange Severe Hypoglycemia in Older Adults With Type 1 Diabetes Study Group.

OBJECTIVE:
Severe hypoglycemia is common in older adults with long-standing type 1 diabetes, but little is known about factors associated with its occurrence.
RESEARCH DESIGN AND METHODS:
A case-control study was conducted at 18 diabetes centers in the T1D Exchange Clinic Network. Participants were ≥60 years old with type 1 diabetes for ≥20 years. Case subjects (n = 101) had at least one severe hypoglycemic event in the prior 12 months. Control subjects (n = 100), frequency-matched to case subjects by age, had no severe hypoglycemia in the prior 3 years. Data were analyzed for cognitive and functional abilities, social support, depression, hypoglycemia unawareness, various aspects of diabetes management, C-peptide level, glycated hemoglobin level, and blinded continuous glucose monitoring (CGM) metrics.
RESULTS:
Glycated hemoglobin (mean 7.8% vs. 7.7%) and CGM-measured mean glucose (175 vs. 175 mg/dL) were similar between case and control subjects. More case than control subjects had hypoglycemia unawareness: only 11% of case subjects compared with 43% of control subjects reported always having symptoms associated with low blood glucose levels (P < 0.001). Case subjects had greater glucose variability than control subjects (P = 0.008) and experienced CGM glucose levels <60 mg/dL for ≥20 min on 46% of days compared with 33% of days in control subjects (P = 0.10). On certain cognitive tests, case subjects scored worse than control subjects.
CONCLUSIONS:
In older adults with long-standing type 1 diabetes, greater hypoglycemia unawareness and glucose variability are associated with an increased risk of severehypoglycemia. A study to assess interventions to prevent severe hypoglycemia in high-risk individuals is neede.

Diabetes Care. 2016 Sep;39(9):1519-26. doi: 10.2337/dc15-2849. Epub 2016 Jul 6.

Elevations in the Fasting Serum Proinsulin-to-C-Peptide Ratio Precede the Onset of Type 1 Diabetes.

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Abstract

OBJECTIVE:

We tested whether an elevation in the serum proinsulin-to-C-peptide ratio (PI:C), a biomarker of β-cell endoplasmic reticulum (ER) dysfunction, was associated with progression to type 1 diabetes.

RESEARCH DESIGN AND METHODS:

Fasting total PI and C levels were measured in banked serum samples obtained from TrialNet Pathway to Prevention (PTP) participants, a cohort of autoantibody-positive relatives without diabetes of individuals with type 1 diabetes. Samples were obtained ∼12 months before diabetes onset from PTP progressors in whom diabetes developed (n = 60), and were compared with age-, sex-, and BMI-matched nonprogressors who remained normoglycemic (n = 58). PI:C ratios were calculated as molar ratios and were multiplied by 100% to obtain PI levels as a percentage of C levels.

RESULTS:

Although absolute PI levels did not differ between groups, PI:C ratios were significantly increased in antibody-positive subjects in whom there was progression to diabetes compared

with nonprogressors (median 1.81% vs. 1.17%, P = 0.03). The difference between groups was most pronounced in subjects who were ≤10 years old, where the median progressor PI:C ratio was nearly triple that of nonprogressors; 90.0% of subjects in this age group within the upper PI:C quartile progressed to the development of diabetes. Logistic regression analysis, adjusted for age and BMI, demonstrated increased odds of progression for higher natural log PI:C ratio values (odds ratio 1.44, 95% CI 1.02, 2.05).

CONCLUSIONS:

These data suggest that β-cell ER dysfunction precedes type 1 diabetes onset, especially in younger children. Elevations in the serum PI:C ratio may have utility in predicting the onset of type 1 diabetes in the presymptomatic phase

Nutr Metab Cardiovasc Dis. 2016 Dec;26(12):1112-1119. doi: 10.1016/j.numecd.2016.08.002. Epub 2016 Aug 6.

Switching from twice-daily glargine or detemir to once-daily degludec improves glucose control in type 1 diabetes. An observational study.

Galasso S[1], Facchinetti A[2], Bonora BM[1], Mariano V[1], Boscari F[1], Cipponeri E[1], Maran A[1], Avogaro A[1], Fadini GP[1], Bruttomesso D[3].

BACKGROUND AND AIMS:
Degludec is an ultralong-acting insulin analogue with a flat and reproducible pharmacodynamic profile. As some patients with type 1 diabetes (T1D) fail to achieve 24-h coverage with glargine or detemir despite twice-daily injections, we studied the effect of switching T1D patients from twice-daily glargine or detemir to degludec.
METHODS AND RESULTS:
In this prospective observational study, T1D patients on twice-daily glargine or detemir were enrolled. At baseline and 12 weeks after switching to degludec, we recorded HbA1c, insulin dose, 30-day blood glucose self monitoring (SMBG) or 14-day continuous glucose monitoring (CGM), treatment satisfaction (DTSQ), fear of hypoglycemia (FHS). We included 29 patients (mean age 34 ± 11 years; diabetes duration 18 ± 10 years).
After switching to degludec, HbA1c decreased from 7.9 ± 0.6% (63 ± 6 mmol/mol) to 7.7 ± 0.6% (61 ± 6 mmol/mol; p = 0.028). SMBG showed significant reductions in the percent and number of blood glucose values <70 mg/dl and in the low blood glucose index (LBGI) during nighttime. CGM showed a significant reduction of time spent in hypoglycemia, an increase in daytime spent in target 70-180 mg/dl, and a reduction in glucose variability.
Total insulin dose declined by 17% (p < 0.001), with 24% reduction in basal and 10% reduction in prandial insulin. DTSQ and FHS significantly improved.
CONCLUSION:
Switching from twice-daily glargine or detemir to once daily degludec improved HbA1c, glucose profile, hypoglycemia risk and treatment satisfaction, while insulin doses decreased.

ClinicalTrials.govNCT02360254.

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Degludec is superior to glargine in terms of daily glycemic variability in people with type 1 diabetes mellitus.

Yamamoto C[1], Miyoshi H, Fujiwara Y, Kameda R, Ichiyama M, Nomoto H, Kameda H, Nakamura A, Atsumi T.

To investigate the differences in glycemic variability between the long-acting insulins glargine and degludec using continuous glucose monitoring, we conducted an open-label, multicenter, prospective, observational study that enrolled 21 participants with type 1 diabetes mellitus currently receiving basal-bolus insulin therapy with glargine. To avoid the potential influence of diet and exercise on glycemic control, all participants were housed and monitored within the hospital for the duration of the study. Once glycemic control was achieved with glargine, glycemic variability was evaluated using continuous glucose monitoring for 3 days. Glargine was then replaced by degludec and glycemic variability again assessed via continuous glucose monitoring. The primary outcome measure of mean amplitude of glycemic excursions was significantly reduced with degludec ($p = 0.028$), as was area under the curve for daily blood glucose level <70 mg/dL ($p = 0.046$). The required insulin dose was reduced up to 25% in the degludec group, although 24-h mean glucose concentrations were not different between groups. In conclusion, once or twice daily glargine was successfully replaced by a daily injection of degludec. When replacing glargine with degludec, a lower dose should be utilized to avoid hypoglycemia. Degludec is an effective and promising long-acting insulin that reduced hypoglycemia and daily blood glucose variability in participants with type 1 diabetes.

Lancet Diabetes Endocrinol. 2016 Mar;4(3):221-32. doi: 10.1016/S2213-8587(15)00436-2. Epub 2015 Dec 3.

Efficacy and safety of liraglutide for overweight adult patients with type 1 diabetes and insufficient glycaemic control (Lira-1): a randomised, double-blind, placebo-controlled trial.

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BACKGROUND:
The combination of insulin and glucagon-like peptide-1 (GLP-1) receptor agonist therapy improves glycaemic control, induces weight loss, and reduces insulin dose needed in type 2 diabetes. We assessed the efficacy and safety of the GLP-1 receptor agonist liraglutide as an add-on therapy to insulin for overweight adult patients with type 1 diabetes.
METHODS:
We did a randomised, double-blind, placebo-controlled trial at Steno Diabetes Center (Gentofte, Denmark). Patients aged 18 years or older with type 1 diabetes, insufficient glycaemic control (HbA1c >8% [64 mmol/mol]), and overweight (BMI >25 kg/m(2)) were randomly assigned (1:1) to receive insulin treatment plus either liraglutide or placebo (saline solution) by subcutaneous injection once per day. Randomisation was done in blocks of four. Treatment assignment was masked to investigators and patients. Treatment lasted 24 weeks and liraglutide was started at a dose of 0·6 mg per day, escalated to 1·2 mg per day after 1 week, and then again to 1·8 mg per day after another week. Intervals between dose increments could be extended at the discretion of the investigator. The primary endpoint was change in HbA1c from baseline to week 24. Secondary endpoints were changes in hypoglycaemic events, glycaemic variability, glycaemic excursions, insulin dose, bodyweight, postprandial plasma concentrations of glucagon and GLP-1, gastric emptying, blood pressure, heart rate, patient-reported outcome measures, time spent in hypoglycaemia, near-normoglycaemia, and hyperglycaemia, plasma fasting glucose, mean glucose, and cholesterol. Efficacy analyses were calculated by use of a mixed model, whereby a patient's data are used as long as the patient is in the study. The safety analyses were done in the intention-to-treat population, which consisted of all patients who received at least one dose of their randomly assigned study drug. This study is registered with ClinicalTrials.gov, number NCT01612468.
FINDINGS:
Between July 10, 2012, and May 30, 2014, we enrolled 100 patients with type 1 diabetes, with 50 patients allocated liraglutide and 50 to placebo. Four patients from the liraglutide group and six patients from the placebo group discontinued treatment before 24 weeks. At the end of treatment, change in HbA1c from baseline did not differ between groups (-0·5%, 95% CI -0·8 to -0·4 [-6·0 mmol/mol, 95% CI -8·7 to -4·4] with liraglutide vs -0·3%, -0·6 to -0·2 [-4·0 mmol/mol, -6·6 to -2·3] with placebo; between-group difference -0·2% [-0·5 to 0·1; 2·2

mmol/mol, -5·5 to 1·1], p=0·1833). The number of hypoglycaemic events was reduced with liraglutide, with an incident rate ratio of 0·82 (95% CI 0·74 to 0·90). However, we detected no changes in glycaemic variability (continuous overall net glycaemic action per 60 min from 10·3 [95% CI 9·8 to 10·8] to 9·9 [9·2 to 10·6] in the liraglutide treated patients vs 10·2 [9·7 to 10·7] to 9·7 [9·1 to 10·3] in the placebo treated patients). Both bolus insulin (difference -5·8 IU, 95% CI -10·7 to -0·8, p=0·0227) and bodyweight (difference -6·8 kg, 95% CI -12·2 to -1·4, p=0·0145) decreased with liraglutide treatment compared with placebo. Heart rate increased with liraglutide, with a difference between groups of 7·5 bpm (95% CI 2·8-12·2, p=0·0019). Postprandial plasma glucagon and GLP-1 concentrations did not differ between groups (difference between groups at end of treatment: -408 mmol/L per 240 min [95% CI -941 to 125, p=0·1309] for glucagon and -266 mmol/L per 240 min [-1034 to 501, p=0·4899] for GLP-1). Gastric emptying was delayed after 3 weeks of treatment with liraglutide (19·9 min, 95% CI 0·8 to 39·0, p=0·0412), but we detected no difference after 24 weeks of treatment (-1·5 min, -20·5 to 17·6, p=0·8793). Patient-reported outcome measures differed between groups only with respect to perceived frequency of hypoglycaemia, which was higher with placebo, with a difference between groups of -0·6 (95% CI -1·1 to -0·07, p=0·0257). Liraglutide was associated with more frequent nausea (29 [58%] patients with liraglutide vs five [10%] with placebo), dyspepsia (11 [22%] patients with liraglutide vs one [2%] with placebo), diarrhoea (ten [20%] patients with liraglutide vs one [2%] with placebo), decreased appetite (seven patients [14%] with liraglutide vs none with placebo), and vomiting (seven [14%] patients with liraglutide vs one [2%] with placebo).

INTERPRETATION:

In patients with type 1 diabetes, overweight, and insufficient glycaemic control, the reduction in HbA1c did not differ between insulin plus placebo and insulin plus liraglutide treatment. Liraglutide was associated with reductions in hypoglycaemic events, bolus and total insulin dose, and bodyweight, and increased heart rate.

Diabetes Care. 2016 Jun;39(6):1027-35. doi: 10.2337/dc15-1136. Epub 2016 Apr 5.

Addition of Liraglutide to Insulin in Patients With Type 1 Diabetes: A Randomized Placebo-Controlled Clinical Trial of 12 Weeks.

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OBJECTIVE:

To investigate whether addition of three different doses of liraglutide to insulin in patients with type 1 diabetes (T1D) results in significant reduction in glycemia, body weight, and insulin dose.

RESEARCH DESIGN AND METHODS:

We randomized 72 patients (placebo = 18, liraglutide = 54) with T1D to receive placebo and 0.6, 1.2, and 1.8 mg liraglutide daily for 12 weeks.

RESULTS:

In the 1.2-mg and 1.8-mg groups, the mean weekly reduction in average blood glucose was -0.55 ± 0.11 mmol/L (10 ± 2 mg/dL) and -0.55 ± 0.05 mmol/L (10 ± 1 mg/dL), respectively ($P < 0.0001$), while it remained unchanged in the 0.6-mg and placebo groups. In the 1.2-mg group, HbA1c fell significantly (-0.78 ± 15%, -8.5 ± 1.6 mmol/mol, $P < 0.01$), while it did not in the 1.8-mg group (-0.42 ± 0.15%, -4.6 ± 1.6 mmol/mol, $P = 0.39$) and 0.6-mg group (-0.26 ± 0.17%, -2.8 ± 1.9 mmol/mol, $P = 0.81$) vs. the placebo group (-0.3 ± 0.15%, -3.3 ± 1.6 mmol/mol). Glycemic variability was reduced by 5 ± 1% ($P < 0.01$) in the 1.2-mg group only. Total daily insulin dose fell significantly only in the 1.2-mg and 1.8-mg groups ($P < 0.05$). There was a 5 ± 1 kg weight loss in the two higher-dose groups ($P < 0.05$) and by 2.7 ± 0.6 kg ($P < 0.01$) in the 0.6-mg group vs. none in the placebo group. In the 1.2- and 1.8-mg groups, postprandial plasma glucagon concentration fell by 72 ± 12% and 47 ± 12%, respectively ($P < 0.05$). Liraglutide led to higher gastrointestinal adverse events ($P < 0.05$) and ≤1% increases (not significant) in percent time spent in hypoglycemia (<55 mg/dL, 3.05 mmol/L).

CONCLUSIONS:

Addition of 1.2 mg and 1.8 mg liraglutide to insulin over a 12-week period in overweight and obese patients with T1D results in modest reductions of weekly mean glucose levels with significant weight loss, small insulin dose reductions, and frequent gastrointestinal side effects. These findings do not justify the use of liraglutide in all patients with T1D.

Diabetes Care. 2016 Apr;39(4):518-24. doi: 10.2337/dc15-2189. Epub 2016 Feb 9.

Extra-Virgin Olive Oil Reduces Glycemic Response to a High-Glycemic Index Meal in Patients With Type 1 Diabetes: A Randomized Controlled Trial.

Bozzetto L[1], Alderisio A[1], Giorgini M[1], Barone F[1], Giacco A[1], Riccardi G[1], Rivellese AA[2], Annuzzi G[1].

OBJECTIVE:
To evaluate whether fat quality, in the context of meals with high- (HGI) or low-glycemic index (LGI), influences postprandial blood glucose (PPG) response in patients with type 1 diabetes.
RESEARCH DESIGN AND METHODS:
According to a randomized crossover design, 13 patients with type 1 diabetes on insulin pump consumed two series (HGI or LGI) of meals with the same carbohydrate quantity while differing for amount and quality of fat: 1) low in fat ("low fat"), 2) high in saturated fat (butter), or 3) high in monounsaturated fat (extra-virgin olive oil) (EVOO). Premeal insulin doses were based on insulin-to-glycemic load ratios. Continuous glucose monitoring was performed and 6-h PPG evaluated.
RESULTS:
PPG was significantly different between HGI and LGI meals ($P = 0.005$ for time × glycemic index interaction by repeated-measures analysis [RMA]), being significantly higher during the first 3 h after the HGI meals with a later tendency to an opposite pattern. In the context of HGI meals, PPG was significantly lower after EVOO than after low fat or butter ($P < 0.0001$ for time × meal interaction by RMA), with a marked difference in the 0- to 3-h glucose incremental area under the curve between EVOO (mean ± SD 198 ± 274 mmol/L × 180 min) and either low fat (416 ± 329) or butter (398 ± 355) ($P < 0.05$). No significant differences were observed in PPG between the three LGI meals.
CONCLUSIONS:
Carbohydrate quality of a mixed meal influences shape and extent of PPG. Besides, using EVOO in a HGI meal attenuates the early postprandial glucose response observed when this meal is consumed with either low fat or butter. Therefore, an optimal prandial insulin administration would require considering, in addition to the quantity of carbohydrates, the quality of both carbohydrate and fat.

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Short-acting insulin analogues versus regular human insulin for adults with type 1 diabetes mellitus

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Background

Short-acting insulin analogue use for people with diabetes is still controversial, as reflected in many scientific debates.

Objectives

To assess the effects of short-acting insulin analogues versus regular human insulin in adults with type 1 diabetes.

Search methods

We carried out the electronic searches through Ovid simultaneously searching the following databases: Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R) (1946 to 14 April 2015), EMBASE (1988 to 2015, week 15), the Cochrane Central Register of Controlled Trials (CENTRAL; March 2015), ClinicalTrials.gov and the European (EU) Clinical Trials register (both March 2015).

Selection criteria

We included all randomised controlled trials with an intervention duration of at least 24 weeks that compared short-acting insulin analogues with regular human insulins in the treatment of adults with type 1 diabetes who were not pregnant.

Data collection and analysis

Two review authors independently extracted data and assessed trials for risk of bias, and resolved differences by consensus. We graded overall study quality using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) instrument. We used random-effects models for the main analyses and presented the results as odds ratios (OR) with 95% confidence intervals (CI) for dichotomous outcomes.

Main results

We identified nine trials that fulfilled the inclusion criteria including 2693 participants. The duration of interventions ranged from 24 to 52 weeks with a mean of about 37 weeks. The participants showed some diversity, mainly with regard to diabetes duration and inclusion/exclusion criteria. The majority of the trials were carried out in the 1990s and participants were recruited from Europe, North America, Africa and Asia. None of the trials was carried out in a blinded manner so that the risk of performance bias, especially for subjective outcomes such as hypoglycaemia, was present in all of the trials. Furthermore, several trials showed inconsistencies in the reporting of methods and results. The mean difference (MD) in glycosylated haemoglobin A1c (HbA1c) was -0.15% (95% CI -0.2% to -0.1%; P value < 0.00001; 2608 participants; 9 trials; low quality evidence) in favour of insulin analogues. The comparison of the risk of severe hypoglycaemia between the two treatment groups showed an OR of 0.89 (95% CI 0.71 to 1.12; P value = 0.31; 2459 participants; 7 trials; very low quality evidence). For overall hypoglycaemia, also taking into account mild forms of hypoglycaemia, the data were generally of low quality, but also did not indicate substantial group differences. Regarding nocturnal severe hypoglycaemic episodes, two trials reported statistically significant effects in favour of the insulin analogue, insulin aspart. However, due to inconsistent reporting in publications and trial reports, the validity of the result remains questionable. We also found no clear evidence for a substantial effect of insulin analogues on health-related quality of life. However, there were few results only based on subgroups of the trial populations. None of the trials reported substantial effects regarding weight gain or any other adverse events. No trial was designed to investigate possible long-term effects (such as all-cause mortality, diabetic complications), in particular in people with diabetes related complications.

Authors' conclusions

Our analysis suggests only a minor benefit of short-acting insulin analogues on blood glucose control in people with type 1 diabetes. To make conclusions about the effect of short acting insulin analogues on long-term patient-relevant outcomes, long-term efficacy and safety data are needed.

Cochrane Database of Systematic Reviews 2016, Issue 1. Art. No.: CD011281.

Subcutaneous rapid-acting insulin analogues for diabetic ketoacidosis

Andrade-Castellanos CA, Colunga-Lozano LE, Delgado-Figueroa N, Gonzalez-Padilla DA

Background

Diabetic ketoacidosis (DKA) is an acute, life-threatening complication of uncontrolled diabetes that mainly occurs in individuals with autoimmune type 1 diabetes, but it is not uncommon in some people with type 2 diabetes. The treatment of DKA is traditionally accomplished by the administration of intravenous infusion of regular insulin that is initiated in the emergency department and continued in an intensive care unit or a high-dependency unit environment. It is unclear whether people with DKA should be treated with other treatment modalities such as subcutaneous rapid-acting insulin analogues.

Objectives

To assess the effects of subcutaneous rapid-acting insulin analogues for the treatment of diabetic ketoacidosis.

Search methods

We identified eligible trials by searching MEDLINE, PubMed, EMBASE, LILACS, CINAHL, and the Cochrane Library. We searched the trials registers WHO ICTRP Search Portal and ClinicalTrials.gov. The date of last search for all databases was 27 October 2015. We also examined reference lists of included randomised controlled trials (RCTs) and systematic reviews, and contacted trial authors.

Selection criteria

We included trials if they were RCTs comparing subcutaneous rapid-acting insulin analogues versus standard intravenous infusion in
participants with DKA of any age or sex with type 1 or type 2 diabetes, and in pregnant women.

Data collection and analysis

Two review authors independently extracted data, assessed studies for risk of bias, and evaluated overall study quality utilising the GRADE instrument. We assessed the statistical heterogeneity of included studies by visually inspecting forest plots and quantifying the diversity using the I^2 statistic. We synthesised data using random-effects model meta-analysis or descriptive analysis, as appropriate.