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### Policy and Guidance

**National Institute for Health and Care Excellence (NICE)**

**Obesity: identification, assessment and management of overweight and obesity in children, young people and adults**
NICE guidelines [CG189] Published date: November 2014

**VibraTip for testing vibration perception to detect diabetic peripheral neuropathy**
NICE medical technologies guidance [MTG22] Published date: December 2014

### New and Updated Cochrane Systematic Reviews

**New Reviews - November 2014**

- **Anti-vascular endothelial growth factor for proliferative diabetic retinopathy**
- **Laser photocoagulation for proliferative diabetic retinopathy**

**Updated Reviews - December 2014**

- **Patient education for preventing diabetic foot ulceration**

### New from UpToDate

**What's new in endocrinology and diabetes mellitus?**
New additions to UpToDate considered by the editors and authors to be of particular interest. You may need an Athens username and password.

### Journal Articles

Please click on the blue link at the end of the abstract (where available) to access full text. You may need an Athens username and password. To register for an Athens account click [here](#).
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1. Title: A meta-analysis comparing the biochemistry of primary hyperparathyroidism in youths to the biochemistry of primary hyperparathyroidism in adults
Citation: Journal of Clinical Endocrinology and Metabolism, December 2014, vol./is. 99/12(4555-4564), 0021-972X; 1945-7197 (01 Dec 2014)
Author(s): Roizen J., Levine M.A.
Language: English
Abstract: Context: The distinctive presentation of primary hyperparathyroidism (PHPT) in adults and youths suggest that PHPT is a fundamentally different disease in these two groups. Objective: To understand the difference in PHPT between adults and youths we compared the biochemistry of PHPT in these two groups. Design: This study is a systematic review and meta-analysis of retrospective studies published 1966-2014 on PHPT. Data Sources: All studies
Adrenal insufficiency is the clinical manifestation of deficient production or action of glucocorticoids, with or without deficiency also in mineralocorticoids and adrenal androgens. It is a life-threatening disorder that can result from primary adrenal failure or secondary adrenal disease due to impairment of the hypothalamic-pituitary axis. Prompt diagnosis and management are essential. The clinical manifestations of primary adrenal insufficiency result from deficiency of all adrenocortical hormones, but they can also include signs of other concurrent autoimmune conditions. In secondary or tertiary adrenal insufficiency, the clinical picture results from glucocorticoid deficiency only, but manifestations of the primary pathological disorder can also be present. The diagnostic investigation, although well established, can be challenging, especially in patients with secondary or tertiary adrenal insufficiency. We summarise knowledge at this time on the epidemiology, causal mechanisms, pathophysiology, clinical manifestations, diagnosis, and management of this disorder.

Publication type: Journal: Article
Source: EMBASE

Full text: Available *Lancet* at *Lancet*, *The*
4. Title: Assessment of the relative effectiveness and tolerability of treatments of type 2 diabetes mellitus: A network meta-analysis

**Citation:** Clinical Therapeutics, November 2014, vol./is. 36/10(1443-1453), 0149-2918;1879-114X (10 Nov 2014)

**Author(s):** Zintzaras E., Miligkos M., Ziakas P., Balk E.M., Mademtzoglou D., Doxani C., Mprotsis T., Gowri R., Xanthopoulou P., Mpoulimari I., Kokkali C., Dimoulou G., Rodopolou P., Stefanidis I., Kent D.M., Hadjigeorgiou G.M.

**Language:** English

**Abstract:** Purpose: The relative effectiveness and tolerability of treatments for type 2 diabetes mellitus (T2DM) is not well understood because few randomized, controlled trials (RCTs) have compared these treatments directly. The purpose of the present study was to evaluate the relative effectiveness and tolerability of treatments of T2DM. Methods: We performed a network meta-analysis of available RCTs with pharmacologic interventions in T2DM and compared antidiabetic drugs and combination regimens with metformin (the reference drug). Glycemic control (proportion achieving HbA\textsubscript{1c}>1cc<sub>1</sub>) goal) and tolerability (risk of hypoglycemia) were the primary outcomes of interest. Direct and indirect relative effects (unadjusted) were expressed as odds ratios and 95% CIs. Findings: Eight treatments (glucagon-like peptide-1 [GLP-1] agonists plus metformin, sulfonylureas plus metformin, dipeptidyl peptidase-4 [DPP-4] inhibitors plus metformin, colesevelan plus metformin, thiazolidinediones plus metformin, meglitinides plus metformin, alpha-glucosidase inhibitor plus metformin, and rosiglitazone monotherapy) outperformed metformin (direct effects). Triple combinations of GLP-1, thiazolidinedione, insulin, metiglinide, or sulfonylureas added to a metformin backbone improved glycemic control (indirect effects). Higher risk of hypoglycemia was noted for sulfonylureas, alpha-glycosidases, and metiglinides when added to metformin (direct effects). Across indirect effects, only 17% of comparisons yielded less risk of hypoglycemia (70% were worse and 13% were comparable). Implications: Our results point out the relative superiority of 2- and 3-drug combination regimens over metformin and summarize treatment effects and tolerability in a comprehensive manner, which adds to our knowledge regarding T2DM treatment options.

**Publication type:** Journal: Article

**Source:** EMBASE

**Full text:** Available Clinical therapeutics at Clinical Therapeutics

5. Title: Association of the vitamin D binding protein polymorphisms with the risk of type 2 diabetes mellitus: A meta-analysis

**Citation:** BMJ Open, 2014, vol./is. 4/11, 2044-6055 (2014)

**Author(s):** Wang G., Li Y., Li L., Yu F., Cui L., Ba Y., Li W., Wang C.

**Language:** English

**Abstract:** Objective: Previous studies on the association between vitamin D binding protein (DBP) polymorphisms and the risk of type 2 diabetes mellitus (T2DM) have produced conflicting results. The purpose of this meta-analysis was to examine whether DBP polymorphisms are associated with the risk of T2DM. Design: Systematic review and meta-analysis. Methods: All eligible studies were searched and acquired from the Cochrane, Pubmed, ISI, CNKI (Chinese) and Wanfang (Chinese) databases. ORs with corresponding 95% CIs were computed to estimate the association between DBP polymorphisms and T2DM. In addition, heterogeneity test, meta-regression and sensitivity analysis were also conducted. Results: Six studies, which included 1191 cases and 882 controls, met the inclusion criteria and were included in the meta-analysis. The results showed that no significant associations were found between codon 416 and codon 420 polymorphisms in the DBP and the risk of T2DM in the overall analyses. In stratified analysis, significant associations between the codon 420 polymorphism and T2DM were found in Asians (allele Lys vs Thr: OR (95% CI) 1.49 (1.19 to 1.85), genotype Lys/Thr versus Thr/Thr: OR (95% CI) 1.80 (1.36 to 2.38), and Lys/Thr+Lys/Lys versus Thr/Thr: OR (95% CI) 1.81 (1.37 to 2.39), respectively) but not in Caucasians. For the codon 416, the significant association with T2DM was also detected in Asians (genotype Glu/Asp+Glu/Glu vs Asp/Asp: OR (95% CI) 1.36 (1.04 to 1.78)) but not in Caucasians. Conclusions: This meta-analysis demonstrated that the DBP polymorphism was moderately associated with increased susceptibility to T2DM in Asians, but a similar association was not found in Caucasians. It suggested that ethnicity might be the potential factor associated with heterogeneity.

**Publication type:** Journal: Article

**Source:** EMBASE

**Full text:** Available Highwire Press at BMJ Open

6. Title: Associations of genetic variants in/near body mass index-associated genes with type 2 diabetes: A systematic meta-analysis

**Citation:** Clinical Endocrinology, November 2014, vol./is. 81/5(702-710), 0300-0664;1365-2265 (01 Nov 2014)
Abstract: Objective Genome-wide association studies have identified many obesity/body mass index (BMI)-associated loci in Europeans and East Asians. Since then, a large number of studies have investigated the role of BMI-associated loci in the development of type 2 diabetes (T2D). However, the results have been inconsistent. The objective of this study was to investigate the associations of eleven obesity/BMI loci with T2D risk and explore how BMI influences this risk.

Methods We retrieved published literature from PubMed and Embase. The pooled odds ratios (OR) with 95% confidence intervals (CI) were calculated using fixed- or random-effect models. Results In the meta-analysis of 42 studies for 11 obesity/BMI-associated loci, we observed a statistically significant association of the FTO rs9939609 polymorphism (66425 T2D cases/239689 normoglycaemic subjects; P = 100 x 10^-41) and six other variants with T2D risk (17915 T2D cases/27531 normoglycaemic individuals: n = 40629-13001; all P < 0001 for SH2B1 rs7498665, FAIM2 rs7138803, TMEM18 rs7561317, GNPDA2 rs10938397, BDNF rs925946 and NEGR1 rs2568958). After adjustment for BMI, the association remained statistically significant for four of the seven variants (all P < 005 for FTO rs9939609, SH2B1 rs7498665, FAIM2 rs7138803, GNPDA2 rs10938397). Subgroup analysis by ethnicity demonstrated similar results. Conclusions This meta-analysis indicates that several BMI-associated variants are significantly associated with T2D risk. Some variants increase the T2D risk independent of obesity, while others mediate this risk through obesity.

Publication type: Journal: Article
Source: EMBASE

7. Title: Clinical prediction of incident heart failure in type 2 diabetes mellitus in 507,637 patients: A systematic review and meta-analysis

Citation: Circulation, November 2014, vol./is. 130/, 0009-7322 (25 Nov 2014)
Author(s): Wang Y., Negishi T., Negishi K., Marwick T.H.
Language: English
Abstract: Background: Heart failure (CHF) is a major cause of death and disability in pts with type 2 diabetes mellitus (T2DM). Early treatment may improve the prognosis. This study sought to improve the assessment of HF risk in pts with T2DM [Unable to Display Character: -] a step that would be critical for effective HF screening. Methods: A systematic literature search was performed on electronic databases including MEDLINE and EMBASE, using MeSH terms 'heart failure', 'risk factor', 'T2DM', 'cardiac dysfunction', 'stage B heart failure', 'incident heart failure', 'risk assessment', 'risk impact', 'risk score', 'predictor', 'prediction' and related free text terms. The search was limited to human studies in full-length publications in English language journal from 1946 to 2014. Univariate relative risk (RR) and hazard ratio (HR) were derived or abstracted from each study. Results: Twenty-one studies (n=1,111,569, including 507,637 subjects with T2DM) were included in this analysis with a follow-up ranging from 1 to 12 years. Risk variables reported <3 times were included in this meta-analysis; the pooled relative risk for incident HF among patients with T2DM ranged from 1.5-2.5 for atherosclerotic vascular disease (coronary, cerebrovascular, peripheral), use of insulin and thiazolidinediones and hypertension (Table). For risks reported in hazard ratio, the association was greater in insulin use (2.22; 1.82-2.71), followed by 5 years increase in age (1.47; 1.25-1.73) and fasting glucose (1.28; 1.10-1.51 per standard deviation). Conclusion: The overall results of this meta-analysis showed that among patients with T2DM, 11 common clinical variables are associated with significantly increased risk of incident HF. (Table presented).
Publication type: Journal: Conference Abstract
Source: EMBASE
Full text: Available Ovid at Circulation

8. Title: Cohort study: At 15 years of follow-up, bariatric surgery, especially when performed within the first year, is associated with diabetes remission and reduced incidence of microvascular and macrovascular complications

Citation: Evidence-Based Medicine, December 2014, vol./is. 19/6(220), 1356-5524;1473-6810 (01 Dec 2014)
Author(s): Sharma A.M.
Language: English
Publication type: Journal: Article
Source: EMBASE
Full text: Available Highwire Press at Evidence-Based Medicine
9. Title: Comparison of dual-hormone artificial pancreas, single-hormone artificial pancreas, and conventional insulin pump therapy for glycaemic control in patients with type 1 diabetes: an open-label randomised controlled crossover trial.  
Citation: The Lancet Diabetes & Endocrinology, January 2015, vol./is. 3/1(17-26), 2213-8595 (2015 Jan)  
Author(s): Haidar A, Legault L, Messier V, Mitre TM, Leroux C, Rabasa-Lhoret R  
Language: English  
Abstract: BACKGROUND: The artificial pancreas is an emerging technology for the treatment of type 1 diabetes and two configurations have been proposed: single-hormone (insulin alone) and dual-hormone (insulin and glucagon). We aimed to delineate the usefulness of glucagon in the artificial pancreas system. METHODS: We did a randomised crossover trial of dual-hormone artificial pancreas, single-hormone artificial pancreas, and conventional insulin pump therapy (continuous subcutaneous insulin infusion) in participants aged 12 years or older with type 1 diabetes. Participants were assigned in a 1:1:1:1:1:1 ratio with blocked randomisation to the three interventions and attended a research facility for three 24-h study visits. During visits when the patient used the single-hormone artificial pancreas, insulin was delivered based on glucose sensor readings and a predictive dosing algorithm. During dual-hormone artificial pancreas visits, glucagon was also delivered during low or falling glucose. During conventional insulin pump therapy visits, patients received continuous subcutaneous insulin infusion. The study was not masked. The primary outcome was the time for which plasma glucose concentrations were in the target range (40-100 mmol/L for 2 h postprandially and 40-80 mmol/L otherwise). Hypoglycaemic events were defined as plasma glucose concentration of less than 33 mmol/L with symptoms or less than 30 mmol/L irrespective of symptoms. Analysis was by modified intention to treat, in which we included data for all patients who completed at least two visits. A p value of less than 0.0167 (005/3) was regarded as significant. This trial is registered with ClinicalTrials.gov, number NCT01754337. FINDINGS: The mean proportion of time spent in the plasma glucose target range over 24 h was 62% (SD 18), 63% (18), and 51% (19) with single-hormone artificial pancreas, dual-hormone artificial pancreas, and conventional insulin pump therapy, respectively. The mean difference in time spent in the target range between single-hormone artificial pancreas and conventional insulin pump therapy was 11% (17; p=0002) and between dual-hormone artificial pancreas and conventional insulin pump therapy was 12% (21; p=0001). There was no difference (15; p=075) in the proportion of time spent in the target range between the single-hormone and dual-hormone artificial pancreas systems. There were 52 hypoglycaemic events with conventional insulin pump therapy (12 of which were symptomatic), 13 with the single-hormone artificial pancreas (five of which were symptomatic), and nine with the dual-hormone artificial pancreas (0 of which were symptomatic); the number of nocturnal hypoglycaemic events was 13 (0 symptomatic), 0, and 0, respectively. INTERPRETATION: Single-hormone and dual-hormone artificial pancreas systems both provided better glycaemic control than did conventional insulin pump therapy. The single-hormone artificial pancreas might be sufficient for hypoglycaemia-free overnight glycaemic control. FUNDING: Canadian Diabetes Association; Fondation J A De Seve; Juvenile Diabetes Research Foundation; and Medtronic. Copyright © 2015 Elsevier Ltd. 
Publication type: Journal Article  
Source: MEDLINE

10. Title: Dietary restriction and exercise for diabetic patients with chronic kidney disease: A systematic review  
Citation: PLoS ONE, November 2014, vol./is. 9/11, 1932-6203 (25 Nov 2014)  
Author(s): Van Huffel L., Tomson C.R.V., Ruige J., Nistor I., Van Biesen W., Bolignano D.  
Language: English  
Abstract: Background: Obesity and sedentary lifestyle are major health problems and key features to develop cardiovascular disease. Data on the effects of lifestyle interventions in diabetics with chronic kidney disease (CKD) have been conflicting. Study Design: Systematic review. Population: Diabetes patients with CKD stage 3 to 5. Search Strategy and Sources: Medline, Embase and Central were searched to identify papers. Intervention: Effect of a negative energy balance on hard outcomes in diabetics with CKD. Outcomes: Death, cardiovascular events, proteinuria, kidney function, metabolic parameters and body composition. Results: We retained 11 studies. There are insufficient data to evaluate the effect on mortality to promote negative energy balance. None of the studies reported a difference in incidence of Major Adverse Cardiovascular Events. Reduction of energy intake does not alter creatinine clearance but significantly reduces proteinuria (mean difference from -0.66 to -1.77 g/24 h). Interventions with combined exercise and diet resulted in a slower decline of eGFR (-9.2 vs. -20.7 mL/min over two year observation; p=0.001). Aerobic and resistance exercise reduced HbA1c (-0.51 (-0.87 to -0.14); p=0.007 and -0.38 (-0.72 to -0.22); p=0.038, respectively). Exercise interventions improve the overall functional status and quality of life in this subgroup. Aerobic exercise reduces BMI (-0.74% (-1.29 to -0.18); p=0.009) and body weight (-2.2 kg (-3.9 to -0.6); p=0.008). Resistance exercise reduces trunk fat mass (-0.7+0.1 vs. +0.8 kg +0.1 kg; p=0.001-0.005). In none of the studies did the intervention cause an increase in adverse events. Limitations: All studies used a different
intervention type and mixed patient groups. Conclusions: There is insufficient evidence to evaluate the effect of negative energy balance interventions on mortality in diabetic patients with advanced CKD. Overall, these interventions have beneficial effects on glycaemic control, BMI and body composition, functional status and quality of life, and no harmful effects were observed.

**Publication type:** Journal: Review  
**Source:** EMBASE  
**Full text:** Available ProQuest at PLoS ONE

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**11. Title:** Does intensive glucose control prevent cognitive decline in diabetes? A meta-analysis  
**Citation:** Circulation, November 2014, vol./is. 130/1, 0009-7322 (25 Nov 2014)  
**Author(s):** Oviedo C.A.P., Martinez M.C.D., Zambrano D.A.M., Mendoza M.P., Jurado M.B., Tamariz L., Vasquez R.A.S.  
**Language:** English  
**Abstract:** Abstract Background: Long term diabetes is associated with cognitive decline. Blood glucose control improves outcomes in patients with diabetes, it is unclear if intensive glucose control prevents cognitive decline. The aim of this study is to conduct a meta-analysis to determine the effects of intensive glucose control on cognitive decline in patients with diabetes. Methods: We searched the MEDLINE database (1966 to December 2013) and supplemented the search with manual searches of bibliographies of key relevant articles. Keywords used for the search were: diabetes mellitus, cognitive decline, cognitive function, cognitive impairment, and glucose control. We selected all randomized studies where a measurement of cognitive decline and the level of glucose control were reported in patients with diabetes. We calculated the weighted standardized mean difference (SMD) of the measurement of cognitive decline between the intensive and standard glucose control arm. We also conducted meta-regression to evaluate the effect of the type of diabetes had on the results and stratified the analysis by type of diabetes. Results: The search strategy yielded 260 studies, of which only 7 met our eligibility criteria. Only three studies included subjects with type 2 diabetes, patients with type 2 diabetes had a median age of 62(59-63), 48(42-60) were female, the median HbA1c was 8% and the median duration of diabetes was 9 years. We included four studies with type 1 diabetes with a median age of 27(16-29) years, 49(49-50)% were female, the median Hba1c was 9% and the median duration of diabetes was 6(5-18) years. The weighted SMD of each cognitive test is shown in Table 1. Conclusions: Intensive glucose control prevents cognitive decline. The largest improvements were seen in the memory and speed processing domains. This was seen mostly in middle-aged type 2 diabetics with diabetes for 9 years and slightly out of control HbA1c.  
**Publication type:** Journal: Conference Abstract  
**Source:** EMBASE  
**Full text:** Available Ovid at Circulation  
**Full text:** Available Ovid at Circulation

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**12. Title:** Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naive patients with type 2 diabetes.  
**Citation:** The Lancet Diabetes & Endocrinology, November 2014, vol./is. 2/11(885-93), 2213-8595 (2014 Nov)  
**Author(s):** Gough SC, Bode B, Woo V, Rodbard HW, Linjawi S, Poulsen P, Damgaard LH, Buse JB, NN9068-3697 (DUAL-l) trial investigators  
**Language:** English  
**Abstract:** BACKGROUND: A fixed-ratio combination of the basal insulin analogue insulin degludec and the glucagon-like peptide-1 (GLP-1) analogue liraglutide has been developed as a once-daily injection for the treatment of type 2 diabetes. We aimed to compare combined insulin degludec-liraglutide (IDegLira) with its components given alone in insulin-naive patients.METHODS: In this phase 3, 26-week, open-label, randomised trial, adults with type 2 diabetes, HbA1c of 7-10% (inclusive), a BMI of 40 kg/m(2) or less, and treated with metformin with or without pioglitazone were randomly assigned (2:1:1) to daily injections of IDegLira, insulin degludec, or liraglutide (18 mg per day). IDegLira and insulin degludec were titrated to achieve a self-measured prebreakfast plasma glucose concentration of 4-5 mmol/L. The primary endpoint was change in HbA1c after 26 weeks of treatment, and the main objective was to assess the non-inferiority of IDegLira to insulin degludec (with an upper 95% CI margin of 03%), and the superiority of IDegLira to liraglutide (with a lower 95% CI margin of 0%). This study is registered with ClinicalTrials.gov, number NCT01336023.FINDINGS: 1663 adults (mean age 55 years [SD 10], HbA1c 83% [09], and BMI 312 kg/m(2) [48]) were randomly assigned, 834 to IDegLira, 414 to insulin degludec, and 415 to liraglutide. After 26 weeks, mean HbA1c had decreased by 19% (SD 11) to 64% (10) with IDegLira, by 14% (10) to 69% (11) with insulin degludec, and by 13% (11) to 70% (12) with liraglutide. IDegLira was non-inferior to insulin degludec (estimated treatment difference -047%,
95% CI -058 to -036, p<00001) and superior to liraglutide (-064%, -075 to -053, p<00001). IDegLira was generally well tolerated; fewer participants in the IDegLira group than in the liraglutide group reported gastrointestinal adverse events (nausea 88 vs 19%), although the insulin degludec group had the fewest participants with gastrointestinal adverse events (nausea 36%). We noted no clinically relevant differences between treatments with respect to standard safety assessments, and the safety profile of IDegLira reflected those of its component parts. The number of confirmed hypoglycaemic events per patient year was 18 for IDegLira, 02 for liraglutide, and 26 for insulin degludec. Serious adverse events occurred in 19 (2%) of 825 patients in the IDegLira group, eight (2%) of 412 in the insulin degludec group, and 14 (3%) of 412 in the liraglutide group. INTERPRETATION: IDegLira combines the clinical advantages of basal insulin and GLP-1 receptor agonist treatment, resulting in improved glycaemic control compared with its components given alone. FUNDING: Novo Nordisk. Copyright 2014 Elsevier Ltd. All rights reserved.

**Publication type:** Journal Article

**Source:** MEDLINE

### 13. Title: Efficacy of standard and intensive statin treatment for the secondary prevention of cardiovascular and cerebrovascular events in diabetes patients: A meta-analysis

**Citation:** PLoS ONE, November 2014, vol./is. 9/11, 1932-6203 (05 Nov 2014)

**Author(s):** De Vries F.M., Kolthof J., Postma M.J., Denig P., Hak E.

**Language:** English

**Abstract:** Results: Five trials were included in the analysis comparing standard-dose statins with placebo with a total of 4 351 participants. Four trials were included for comparing standard-dose with intensive-dose statins, including 4 805 participants. Compared with placebo, standard-dose statin treatment resulted in a significant relative risk (RR) reduction of 15% in the occurrence of any major cardiovascular or cerebrovascular event (RR 0.85, 95% CI 0.79-0.91). Compared with standard-dose statin treatment, intensive-dose statin treatment resulted in an additional 9% relative risk reduction (RR 0.91, 95% CI 0.84-0.98). Conclusion: Treatment with standard-dose statins to prevent cardiovascular or cerebrovascular events in diabetes patients with manifest cardiovascular disease results in an estimated 15% relative risk reduction and intensive-dose statin treatment adds 9%. If proven cost-effective, more intensive statin treatment should be recommended for diabetes patients at high cardiovascular risk.

Aims: To estimate the efficacy of standard and intensive statin treatment in the secondary prevention of major cardiovascular and cerebrovascular events in diabetes patients. Copyright: Methods: A systematic search was conducted in Medline over the years 1990 to September 2013. Randomized, doubleblind, clinical trials comparing a standard-dose statin with placebo or a standard-dose statin with an intensive-dose statin for the secondary prevention of cardiovascular and cerebrovascular events in diabetes patients were selected. Trial and patient characteristics were extracted independently by two researchers. The combined effect on the composite primary endpoint was measured with a fixed-effect model. Potential publication bias was examined with a funnel plot.

**Publication type:** Journal: Article

**Source:** EMBASE

**Full text:** Available ProQuest at PLoS ONE

**Full text:** Available ProQuest at PLoS One

### 14. Title: Glycemic control and excess mortality in type 1 diabetes

**Citation:** New England Journal of Medicine, November 2014, vol./is. 371/21(1972-1982), 0028-4793;1533-4406 (20 Nov 2014)

**Author(s):** Lind M., Svensson A.-M., Kosiborod M., Gudbjornsdottr S., Pivodic A., Wedel H., Dahlqvist S., Clements M., Rosengren A.

**Language:** English

**Abstract:** BACKGROUND: The excess risk of death from any cause and of death from cardiovascular causes is unknown among patients with type 1 diabetes and various levels of glycemic control. We conducted a registry-based observational study to determine the excess risk of death according to the level of glycemic control in a Swedish population of patients with diabetes. METHODS: We included in our study patients with type 1 diabetes registered in the Swedish National Diabetes Register after January 1, 1998. For each patient, five controls were randomly selected from the general population and matched according to age, sex, and county. Patients and controls were followed until December 31, 2011, through the Swedish Register for Cause-Specific Mortality. RESULTS: The mean age of the patients with diabetes and the controls at baseline was 35.8 and 35.7 years, respectively, and 45.1% of the participants in each group were women. The mean follow-up in the diabetes and control groups was 8.0 and 8.3 years, respectively. Overall, 2701 of 33,915 patients with diabetes (8.0%) died, as compared with 4835 of 169,249 controls (2.9%) (adjusted hazard ratio, 3.52; 95% confidence interval [CI], 3.06 to 4.04); the corresponding rates of death from cardiovascular causes were 2.7% and 0.9% (adjusted hazard ratio, 4.60; 95% CI, 3.47 to 6.10). The
multivariable-adjusted hazard ratios for death from any cause according to the glycated hemoglobin level for patients with diabetes as compared with controls were 2.36 (95% CI, 1.97 to 2.83) for a glycated hemoglobin level of 6.9% or lower (<52 mmol per mole), 2.38 (95% CI, 2.02 to 2.80) for a level of 7.0 to 7.8% (53 to 62 mmol per mole), 3.11 (95% CI, 2.66 to 3.62) for a level of 7.9 to 8.7% (63 to 72 mmol per mole), 3.65 (95% CI, 3.11 to 4.30) for a level of 8.8 to 9.6% (73 to 82 mmol per mole), and 8.51 (95% CI, 7.24 to 10.01) for a level of 9.7% or higher (>83 mmol per mole). Corresponding hazard ratios for death from cardiovascular causes were 2.92 (95% CI, 2.07 to 4.13), 3.39 (95% CI, 2.49 to 4.61), 4.44 (95% CI, 3.32 to 5.96), 5.35 (95% CI, 3.94 to 7.26), and 10.46 (95% CI, 7.62 to 14.37). CONCLUSIONS: In our registry-based observational study, patients with type 1 diabetes and a glycated hemoglobin level of 6.9% or lower had a risk of death from any cause or from cardiovascular causes that was twice as high as the risk for matched controls.

**Publication type:** Journal: Article  
**Source:** EMBASE  
**Full text:** Available *Massachusetts Medical Society* at *New England Journal of Medicine* (NEJM)

**15. Title:** HbA1C variability and the risk of renal status progression in diabetes mellitus: A meta-analysis  
**Citation:** PLoS ONE, December 2014, vol./is. 9/12, 1932-6203 (18 Dec 2014)  
**Author(s):** Dongsheng C., Yang Fei., Yumei L., Junhui L., Qin X., Xiaoxia W., Niansong W.  
**Language:** English  
**Abstract:** Objective: To explore the association between glycated hemoglobin (A1C) variability and renal disease progression in patients with diabetes mellitus. Methods: A comprehensive search was performed using the PubMed and Embase databases (up to April 26, 2014). The hazard ratio (HR) was pooled per unit increase in the standard deviation of A1C (A1C-SD) to evaluate the dose-response relationship between A1C-SD and the risk of nephropathy. Results: Eight studies with a total of 17,758 subjects provided the HR for A1C-SD and were included in the final meta-analysis. The pooled HR results demonstrated that A1C-SD was significantly associated with the progression of renal status (HR for both T1DM and T2DM 1.43, 95% confidence interval [CI] 1.24-1.64; HR for T1DM 1.70, 95%CI 1.41-2.05; HR for T2DM 1.20, 95%CI 1.12-1.28). A1C-SD was significantly correlated with new-onset microalbuminuria (HR for T1DM 1.63, 95%CI 1.28-2.07; HR for T2DM 1.23, 95%CI 1.08-1.39). These outcomes were also supported in subgroup analyses. Furthermore, sensitivity analyses demonstrated that the results were robust. Conclusions: A1C variability is independently associated with the development of microalbuminuria and the progression of renal status in both type 1 and 2 diabetes patients. A standard method for measuring A1C variability is essential for further and deeper analyses. In addition, future studies should assess the effect of reducing A1C variability on nephropathy complication.  
**Publication type:** Journal: Article  
**Source:** EMBASE  
**Full text:** Available *ProQuest* at PLoS ONE

**16. Title:** Home use of closed-loop insulin delivery for overnight glucose control in adults with type 1 diabetes: a 4-week, multicentre, randomised crossover study.  
**Citation:** The Lancet Diabetes & Endocrinology, September 2014, vol./is. 2/9(701-9), 2213-8595 (2014 Sep)  
**Language:** English  
**Abstract:** BACKGROUND: Closed-loop insulin delivery is a promising option to improve glycaemic control and reduce the risk of hypoglycaemia. We aimed to assess whether overnight home use of automated closed-loop insulin delivery would improve glucose control. METHODS: We did this open-label, multicentre, randomised controlled, crossover study between Dec 1, 2012, and Dec 23, 2014, recruiting patients from three centres in the UK. Patients aged 18 years or older with type 1 diabetes were randomly assigned to receive 4 weeks of overnight closed-loop insulin delivery (using a model-predictive control algorithm to direct insulin delivery), then 4 weeks of insulin pump therapy (in which participants used real-time display of continuous glucose monitoring independent of their pumps as control), or vice versa. Allocation to initial treatment group was by computer-generated permuted block randomisation. Each treatment period was separated by a 3-4 week washout period. The primary outcome was time spent in the target glucose range of 39-80 mmol/L between 0000 h and 0700 h. Analyses were by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01440140. FINDINGS: We randomly assigned 25 participants to initial treatment in either the closed-loop group or the control group, patients were later crossed over into the other group; one patient from the closed-loop group withdrew consent after randomisation, and data
for 24 patients were analysed. Closed loop was used over a median of 83 h (IQR 60-96) on 555 (86%) of 644 nights. The proportion of time when overnight glucose was in target range was significantly higher during the closed-loop period compared to during the control period (mean difference between groups 135%, 95% CI 73-197; p=00002). We noted no severe hypoglycaemic episodes during the control period compared with two episodes during the closed-loop period; these episodes were not related to closed-loop algorithm instructions. INTERPRETATION: Unsupervised overnight closed-loop insulin delivery at home is feasible and could improve glucose control in adults with type 1 diabetes. FUNDING: Diabetes UK. Copyright 2014 Elsevier Ltd. All rights reserved.

**Publication type:** Journal Article, Research Support, N.I.H., Extramural, Research Support, Non-U.S. Gov't

**Source:** MEDLINE

17. **Title:** Internet Blood Glucose Monitoring Systems Provide Lasting Glycemic Benefit in Type 1 and 2 Diabetes: A Systematic Review

**Citation:** Medical Clinics of North America, January 2015, vol./is. 99/1(17-33), 0025-7125;1557-9859 (01 Jan 2015)

**Author(s):** Tildesley H.D., Po M.D., Ross S.A.

**Language:** English

**Abstract:** Internet blood glucose monitoring systems (IBGMS) are associated with improved glycemic control in patients with type 2 diabetes (T2D) who are pharmacologically managed, using oral agents or insulin. IBGMS improves glycemic levels in patients with type 1 diabetes (T1D). IBGMS has not led to increased hypoglycemia. Mechanisms underlying IBGMS-associated glycemic improvement extend beyond optimizing insulin dose titration. The most important effects seem to be associated with increased patient self-motivation and improved patient-physician communication. IBGMS have been recommended in clinical practice guidelines, and their effectiveness and safety in trials suggest that this approach is appropriate for patients with T1D or T2D.

**Publication type:** Journal: Review

**Source:** EMBASE

18. **Title:** Liraglutide for the Treatment of Type 2 Diabetes Mellitus: A Meta-analysis of Randomized Placebo-Controlled Trials

**Citation:** Advances in Therapy, November 2014, vol./is. 31/11(1182-1195), 0741-238X;1865-8652 (27 Nov 2014)

**Author(s):** Du Q., Wang Y.-J., Yang S., Zhao Y.-Y., Han P.

**Language:** English

**Abstract:** Introduction: Liraglutide has been widely used in the treatment of type 2 diabetes mellitus (T2DM), however, the results of a number of randomized placebo-controlled trials on the effects of liraglutide for the treatment of T2DM have varied. The purpose of this study was to assess the effects of liraglutide versus placebo for the treatment of T2DM. Methods: We searched randomized controlled trials comparing liraglutide and placebo for the treatment of T2DM in the following databases: MEDLINE; EMBASE; Cochrane Library Central Register of Controlled Trials; and Clinical Trials Gov (through August 2014). The standard mean difference (SMD) was calculated for the continuous data and a chi<sup>2</sup> test was used to evaluate heterogeneity. Results: Initially, 103 articles were retrieved through the literature search and 11 studies met the requirements for the meta-analysis. The effects of liraglutide on lowering glycosylated hemoglobin, fasting plasma glucose, reducing weight, lowering blood pressure, and the prevalence of adverse events were significantly different from placebo (P < 0.0001, SMD = -0.96, 95% CI = [-1.20, -0.73]; P < 0.0001, SMD = -0.72, 95% CI = [-0.99, -0.45]; P = 0.004, SMD = -0.24, 95% CI = [-0.40, -0.07]; P = 0.021, SMD = -0.15, 95% CI = [-0.27, -0.02], and P = 0.007, respectively). Conclusion: Liraglutide had greater hypoglycemic, weight-reducing and systolic blood pressure-lowering effects than placebo. However, there were more adverse events in the treatment with liraglutide. It is suggested that additional well-designed, large, studies be conducted to further support the use of liraglutide and provide objective guidance for clinical application of liraglutide.

**Publication type:** Journal: Article

**Source:** EMBASE

19. **Title:** Lixisenatide plus basal insulin in patients with type 2 diabetes mellitus: A meta-analysis

**Citation:** Journal of Diabetes and its Complications, November 2014, vol./is. 28/6(880-886), 1056-8727;1873-460X (01 Nov 2014)

**Author(s):** Charbonnel B., Bertolini M., Tinahones F.J., Domingo M.P., Davies M.

**Language:** English

**Abstract:** Methods: A meta-analysis was performed of results from three trials in the GetGoal clinical program concerning lixisenatide or placebo plus basal insulin with/without OADs. The primary endpoint was change in HbA<sub>1c</sub> from baseline to week 24. Secondary endpoints were change in PPG, FPG, insulin dose, and
weight from baseline to week 24. Hypoglycemia rates and several composite endpoints were assessed. Aims: The efficacy of the once-daily prandial GLP-1 receptor agonist lixisenatide plus basal insulin in T2DM was assessed by pooling results of phase III trials. Results: Lixisenatide plus basal insulin was significantly more effective than basal insulin alone at reducing HbA<sub>1c</sub> at 24 weeks. Composite and secondary endpoints were improved significantly with lixisenatide plus basal insulin, with the exception of FPG, which showed no significant difference between the groups. Lixisenatide plus basal insulin was associated with an increased incidence of hypoglycemia versus basal insulin alone. Conclusions: Lixisenatide plus basal insulin resulted in significant improvement in glycemic control versus basal insulin alone, particularly in terms of controlling PPG. Prandial lixisenatide in combination with basal insulin is a suitable option for treatment intensification in patients with T2DM insufficien...
were stratified according to previous treatment (octreotide or lanreotide) and growth hormone concentrations at screening (25-10 μg/L and >10 μg/L). Patients and study investigators were not masked to study drug assignment but were masked to pasireotide dose allocation. The primary endpoint was number of patients achieving biochemical control, defined as mean growth hormone concentration less than 25 μg/L and normalised IGF-1 concentration. Efficacy analyses were based on intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01137682.FINDINGS: Between Dec 17, 2010, and Aug 6, 2012, 198 patients were enrolled and randomly assigned to pasireotide 40 mg (n=65), pasireotide 60 mg (n=65), or active control (n=68) groups. At 24 weeks, ten (15%) patients in the pasireotide 40 mg group and 13 (20%) patients in the pasireotide 60 mg group achieved biochemical control, compared with no patients in the active control group (absolute difference from control group 154%, 95% CI 76–265, p=0.0006 for pasireotide 40 mg group, 200%, 111–318, p<0.0001 for pasireotide 60 mg group). The most common adverse events were hyperglycaemia (21 [33%] for treatment with 40 mg pasireotide, 19 [31%] with 60 mg pasireotide, and nine [14%] with active control), diabetes (13 [21%], 16 [26%], and five [8%]), and diarrhoea (ten [16%], 12 [19%], and three [5%]); most were grade 1 or 2 in severity. Serious adverse events were reported in six (10%) patients in the pasireotide 40 mg group, two (3%) in the pasireotide 60 mg group, and three (5%) in the active control group. INTERPRETATION: Pasireotide provides superior efficacy compared with continued treatment with octreotide or lanreotide, and could become the new standard pituitary-directed treatment in patients with acromegaly who are inadequately controlled using first-generation somatostatin analogues. FUNDING: Novartis Pharma AG. Financial support for medical editorial assistance was provided by Novartis Pharmaceuticals Corporation. Copyright 2014 Elsevier Ltd. All rights reserved.

**Publication type:** Journal Article  
**Source:** MEDLINE

22. **Title:** Post hoc analysis of RCT: Intensive glucose-lowering results in increased cardiovascular mortality in younger but not older individuals with type 2 diabetes  
**Citation:** Evidence-Based Medicine, December 2014, vol./is. 19/6(210), 1356-5524;1473-6810 (01 Dec 2014)  
**Author(s):** Giorgino F.  
**Language:** English  
**Publication type:** Journal: Article  
**Source:** EMBASE  
**Full text:** Available Highwire Press at Evidence-Based Medicine

23. **Title:** Shining the Light on Sunshine: A systematic review of the influence of sun exposure on type 2 diabetes mellitus-related outcomes  
**Citation:** Clinical Endocrinology, December 2014, vol./is. 81/6(799-811), 0300-0664;1365-2265 (01 Dec 2014)  
**Author(s):** Shore-Lorenti C., Brennan S.L., Sanders K.M., Neale R.E., Lucas R.M., Ebeling P.R.  
**Language:** English  
**Abstract:** Prospective observational studies uniformly link vitamin D deficiency with the incidence of type 2 diabetes mellitus (T2DM), yet trials supplementing participants at risk of T2DM with vitamin D to reduce progression to T2DM have yielded inconsistent results. Inconsistencies between supplementation trials may be due to insufficient dosing or small sample sizes. Observational studies may also have reported spurious associations due to uncontrolled confounding by lifestyle or genetic factors. Alternatively, observational and intervention studies may not be entirely comparable. Observational studies show an association between higher vitamin D status, which is predominantly derived from sun exposure, and decreased incidence of T2DM. Trials intervene with vitamin D supplementation, and therefore may be missing alternate causes of the effect of sun exposure, as seen in observational studies. We propose that sun exposure may be the driving force behind the associations seen in observational studies; sun exposure may have additional benefits beyond increasing serum 25-hydroxyvitamin D (25OHD) levels. We performed an electronic literature search to identify articles that examined associations between sun exposure and T2DM and/or glucose metabolism. A best evidence synthesis was then conducted using outcomes from analyses deemed to have high methodological quality. Ten eligible full-text articles were identified, yielding 19 T2DM-related outcomes. The best evidence analysis considered 11 outcomes which were grouped into six outcome types: T2DM, fasting glucose, glucose tolerance, fasting insulin, insulin secretion and insulin sensitivity. There was moderate evidence to support a role of recreational sun exposure in reducing odds of T2DM incidence. High-level evidence was lacking; evidence presented for other outcomes was of low or insufficient level. This review highlights significant gaps in research pertaining to sun exposure and T2DM-related outcomes. Further research is encouraged as we aim to identify novel preventative strategies for T2DM.  
**Publication type:** Journal: Review  
**Source:** EMBASE
increased risk of microvascular disease. Whether statins are protective against some forms of microvascular disease

Abstract: OBJECTIVE: The aims of this study were to investigate the association between smoking and incident type 2 diabetes, accounting for a large number of potential confounding factors, and to explore potential effect modifiers and intermediate factors. RESEARCH DESIGN AND METHODS: The European Prospective Investigation into Cancer and Nutrition (EPIC)-InterAct is a prospective case-cohort study within eight European countries, including 12,403 cases of incident type 2 diabetes and a random subcohort of 16,835 individuals. After exclusion of individuals with missing data, the analyses included 10,327 cases and 13,863 subcohort individuals. Smoking status was used (never, former, current), with never smokers as the reference. Country-specific Prentice-weighted Cox regression models and random-effects meta-analysis were used to estimate hazard ratios (HRs) for type 2 diabetes. RESULTS: In men, the HRs (95% CI) of type 2 diabetes were 1.40 (1.26, 1.55) for former smokers and 1.43 (1.27, 1.61) for current smokers, independent of age, education, center, physical activity, and alcohol, coffee, and meat consumption. In women, associations were weaker, with HRs (95% CI) of 1.18 (1.07, 1.30) and 1.13 (1.03, 1.25) for former and current smokers, respectively. There was some evidence of effect modification by BMI. The association tended to be slightly stronger in normal weight men compared with those with overall adiposity. CONCLUSIONS: Former and current smoking was associated with a higher risk of incident type 2 diabetes compared with never smoking in men and women, independent of educational level, physical activity, alcohol consumption, and diet. Smoking may be regarded as a modifiable risk factor for type 2 diabetes, and smoking cessation should be encouraged for diabetes prevention.

Abstract: BACKGROUND: The role of statins in the development of microvascular disease in patients with diabetes is unknown. We tested the hypothesis that statin use increases the risk of diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, and gangrene of the foot in individuals with diabetes. METHODS: We identified all patients living in Denmark who were aged 40 years or older and were diagnosed with incident diabetes between Jan 1, 1996, and Dec 31, 2009. We obtained patients' data from the Danish Patient Registry and information on drug use from the Danish Registry of Medicinal Product Statistics. We randomly selected 15 679 individuals from the database who had used statins regularly until their diagnosis of diabetes (statin users) and matched them in a 1:3 ratio with 47 037 individuals who had never used statins before diagnosis (non-statin users). Our primary outcome was to compare the cumulative incidence of diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, or gangrene of the foot in statin users versus non-statin users. We analysed data with Cox regression models, adjusted for covariates including sex, age at diabetes diagnosis, and method of diabetes diagnosis. To address potential biases between statin users and non-statin users, we made adjustments to our analysis with a propensity score and with other factors. Median follow-up was 27 years (range 0-13). FINDINGS: During 215 725 person-years of follow-up, 2866 patients developed diabetic retinopathy, 1406 developed diabetic neuropathy, 1248 developed diabetic nephropathy, and 2392 developed gangrene of the foot. Compared with non-statin users, statin users had a lower cumulative incidence of diabetic retinopathy (hazard ratio 0.60, 95% CI 0.54-0.66; p<0.0001), diabetic neuropathy (0.66, 0.57-0.75; p<0.0001), and gangrene of the foot (0.88, 0.80-0.97; p=0.0010), but not diabetic nephropathy (0.97, 0.85-1.10; p=0.062). These results were similar after adjusting for the competing risk of death, after matching for a propensity score, after adjusting for visits to a family doctor, and by stratification on covariates. The corresponding multivariable adjusted hazard ratio for risk of diabetes in the total population was 117 (95% CI 114-121; p<0.0001). INTERPRETATION: Use of statins before diagnosis of incident diabetes was not associated with an increased risk of microvascular disease. Whether statins are protective against some forms of microvascular disease-
a possibility raised by these data—will need to be addressed in other studies similar to ours, in mendelian randomisation studies, and preferably in randomised controlled trials.

**FUNDING:** Herlev Hospital, Copenhagen University Hospital. Copyright 2014 Elsevier Ltd. All rights reserved.

**Publication type:** Journal Article  
**Source:** MEDLINE

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26. **Title:** Systematic review with meta-analysis: ACE inhibitors are associated with a reduction in all-cause mortality versus angiotensin II receptor blockers in patients with diabetes mellitus  
**Citation:** Evidence-Based Medicine, December 2014, vol./is. 19/6(218), 1356-5524;1473-6810 (01 Dec 2014)  
**Author(s):** Harel Z., Silver S.A.  
**Language:** English  
**Publication type:** Journal: Article  
**Source:** EMBASE  
**Full text:** Available Highwire Press at Evidence-Based Medicine

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**News**

**Vegetarian diet 'could have slight benefits in diabetes'**  
**Monday Nov 24 2014**  
"Vegetable diet will beat diabetes: Meat-free lifestyle cures killer disease," is the typically overblown headline in the Daily Express. But researchers actually found a vegetarian diet led to a quite modest fall in only one measure of blood glucose...

**Can a yoghurt a day reduce diabetes risk?**  
**Tuesday Nov 25 2014**  
"Eating a small portion of yoghurt every day may reduce diabetes risk," The Independent reports. This news comes from a US study that assessed the eating habits of more than 100,000 people and then followed them up every four years, looking...

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