Type 2 Diabetes
Current Awareness Bulletin
June 2019

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Title: Dethroning the king?: The future of metformin as first line therapy in type 2 diabetes

Citation: Journal of Diabetes and its Complications; Jun 2019; vol. 33 (no. 6); p. 462

Author(s): Inzucchi, Silvio E; Fonseca, Vivian

Abstract: More importantly, the new data raises the possibility of a more evidence-based approach to personalizing treatment choices for people with type 2 diabetes. Evidence that metformin is still the best initial therapy for type 2 diabetes. Extensive clinical experience has supported the early use of metformin, a drug that has been available in many countries of the world for decades and which is actually based on a biguanide derived from the French lilac, (Galega officinalis) used in medieval times in Europe as a traditional diabetes treatment. It is generally accepted that the ideal anti-hyperglycemic medication should have high glucose-lowering efficacy with low risk of hypoglycemia and weight gain, be safe and well-tolerated and affordable. Metformin meets many of these characteristics, which explains its position in current therapeutic paradigms. In the US, large retailers offer the drug at a cost of just $4 per month or less. This time-tested remedy is clearly well positioned to continue as foundation therapy for patients with type 2 diabetes, including those with CV disease. Trials with newer medications have enrolled patients with lower baseline A1c. Since the degree of fall in A1c is related to the baseline A1c, newer medications appear to be as efficacious. In patients treated with a GLP-1 receptor agonist liraglutide in the LEADER study, there were a large number of patients with moderate and severe renal impairment who demonstrated not only safety of the drug but also benefit in terms of prevention of cardiovascular events.

Title: Sex differences in the pathogenesis of type 2 diabetes may explain the stronger impact of diabetes on atherosclerotic heart disease in women

Citation: Journal of Diabetes and its Complications; Jun 2019; vol. 33 (no. 6); p. 460

Author(s): Mauvais-Jarvis, Franck

Abstract: A meta-analysis including almost 900,000 individuals reported a 40% greater risk of incident coronary artery disease in diabetic women compared to men with diabetes. The authors concluded that a greater deterioration in and more prolonged exposure to cardiovascular risk factors among prediabetic women compared with men, possibly driven by greater levels of adiposity, may be responsible for the excess risk of diabetes-related coronary artery disease in women. In a cross-sectional study of older adults from the UK (aged 60–79 years), non-diabetic women tended to have more favorable risk factors and were less insulin resistant than non-diabetic men. However, this difference was blunted in the diabetic state. Importantly, this metabolic dysregulation was observed as early as 23 years of age on average and persisted throughout adulthood, up to the age of the diagnosis of diabetes. During the transition from childhood to midlife, women who will develop diabetes are exposed to faster metabolic alterations and higher burden of exposure to increased adiposity, LDL cholesterol, and fasting hyperglycemia than men who will develop diabetes. Thus, accumulating evidence suggests that the excess risk of diabetes-related atherosclerotic heart disease in women is rooted in the biological sex differences between men and women.

Title: Body composition changes in diabetes and aging

Citation: Journal of Diabetes and its Complications; Jun 2019; vol. 33 (no. 6); p. 451

Author(s): Al-Sofiani, Mohammed E; Ganji, Suneeta S; Kalyani, Rita R
Abstract: Aging is associated with changes in body composition, including both fat gain and muscle loss beginning in middle age, and is associated with increased risk of type 2 diabetes. Moreover, changes in fat distribution take place in adults as they age and may contribute to the increased risk of type 2 diabetes. Recent literature has shown differences in the age-related changes in body composition by diabetes status suggesting that some of these changes might not only be a risk factor of the development of diabetes but could also be a consequence of the disease. In this article, we review the current evidence on body composition changes that take place in adults after the diagnosis of type 2 diabetes and compare them to those observed in adults without diabetes as they age. We also review the effect of various lifestyle, pharmacological, and surgical treatments that lower blood glucose on body composition in adults with type 2 diabetes.

Title: Fourth harmonic of radial pulse wave predicts adverse cardiac events in asymptomatic patients with type 2 diabetes

Citation: Journal of Diabetes and its Complications; Jun 2019; vol. 33 (no. 6); p. 413

Author(s): Chi-Wei, Chang; Kuo-meng, Liao; Yi-Ting, Chang; Sheng-Hung, Wang; Ying-chun, Chen; Gin-Chung, Wang

Aims: Studies have shown that the fourth harmonic of the radial pulse wave (C4) is associated with atherosclerotic processes and myocardial ischemia. We sought to investigate whether C4 is an independent predictor of adverse cardiac events (ACE).

Methods: The baseline C4 is calculated using the Fourier series method. 1968 asymptomatic patients with type 2 diabetes were followed up for 1.8 ± 0.4 years and survival analysis were performed using Cox proportional hazard model.

Results: The Cox regression analysis showed that the C4 value is independent and inversely related to ACE both before and after adjusting for age, sex, smoke, systolic blood pressure, dyslipidemia, and Hba1c. (P for trend < 0.001).

Conclusions: Decreasing C4 is associated with an increased risk of ACE in asymptomatic patients with type 2 diabetes.

Title: Effect of a multifactorial intervention on the increase in physical activity in subjects with type 2 diabetes mellitus: a randomized clinical trial (EMID Study)

Citation: European Journal of Cardiovascular Nursing; Jun 2019; vol. 18 (no. 5); p. 399

Author(s): Alonso-Domínguez, Rosario; Patino-Alonso, María C; Sánchez-Aguadero, Natalia; García-Ortiz, Luis; Recio-Rodríguez, Jose I; Gómez-Marcos, Manuel A

Background: Regular physical activity is essential for metabolic control in type 2 diabetes mellitus.

Aims: The aim of this study was to assess the short and long-term impact of a multifactorial intervention on physical activity and clinically relevant biochemical parameters in patients with type 2 diabetes mellitus.

Methods: This randomised, controlled clinical trial (NCT02991079) included two parallel groups aged 25–70 years from a primary care health centre in Salamanca, Spain. The subjects were assigned randomly (1:1) to control and intervention groups, using Epidat 4.0 software. Both were counselled on the importance of physical activity and maintaining a healthy diet. The intervention group also took five low–moderate intensity 4 km nurse-guided walks, received a smartphone application to promote healthy habits and attended a diet workshop. Physical activity was measured objectively using a pedometer and subjectively using a shortened international physical activity questionnaire (at baseline, 3 and 12 months).

Results: In total, 204 subjects were included (mean age 60.6 years, 45.6% were women). After 3 months, relative to the control group, the intervention group increased their daily number of steps by 1852, aerobic steps by 1623, distance walked by 994 m, and total metabolic equivalent minutes per week by 1297 and decreased sedentary time by 34.3 minutes per day. Differences from baseline
persisted at 12 months, including mean increases of 1141 daily steps, 917 aerobic steps, and 1065 total metabolic equivalent minutes per week in the intervention group relative to the control group (P<0.05 for all).

**Conclusions:** The success of this multifactorial intervention should help inform future clinical approaches and application designs towards managing type 2 diabetes mellitus and improving patient outcomes.

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**Title:** Diabetes Prevention Programme Launches

**Citation:** Community Practitioner; Jun 2019; vol. 92 (no. 5); p. 9

**Author(s):** Anonymous

**Abstract:** A program to tackle the increasing prevalence of type 2 diabetes has been launched by the Public Health Agency. Around 96,000 people are living with diabetes in Northern Ireland—a shocking 69.3% increase since 2007. The Diabetes Prevention Programme is aimed at people who have been identified as pre-diabetic—with a blood sugar level slightly above the normal range.

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**Title:** Self-Compassion, Metabolic Control and Health Status in Individuals with Type 2 Diabetes: A UK Observational Study.

**Citation:** Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association; Jun 2019

**Author(s):** Morrison, Amy E; Zaccardi, Francesco; Chatterjee, Sudesna; Brady, Emer; Doherty, Yvonne; Robertson, Noelle; Hadjiconstantinou, Michelle; Daniels, Lois; Hall, Andrew; Khunti, Kamlesh; Davies, Melanie J

**Aims:** Self-compassion is a modifiable characteristic, linked with psychological well being and intrinsic motivation to engage in positive health behaviours. We aimed to explore levels of self-compassion in individuals with type 2 diabetes (T2DM) and their association with levels of depression, diabetes-related distress and glycaemic control.

**Methods:** A cross-sectional study in 176 patients with T2DM in Leicester, UK, using three self-report questionnaires: the Self Compassion Scale (SCS); Patient Health Questionnaire (PHQ-9), and Diabetes Distress Scale (DDS-17). Demographic data, medical history and blood samples were collected.

**Results:** Majority of participants were male (n=120, 68.2%), with median [IQR] age and HbA1c of 66 [60, 71] years and 7.3 [6.7, 8.0] %, respectively. Multivariable analysis adjusting for age, gender, ethnicity and diabetes duration revealed significant association of all three scores with HbA1c: per one standard deviation increase of each score, a -0.16% reduction in HbA1c for SCS (p=0.027), 0.21% increase for PHQ-9 (p=0.012) and 0.33% increase for DDS-17 (p<0.001).

**Conclusions:** Higher levels of self-compassion and lower levels of depressive symptoms were associated with significantly better long-term diabetes control. These results reinforce the importance of emphasis on psychological parameters, including self-compassion, in the multi-disciplinary management of T2DM. We identify this as a potential area for intervention in UK practice.

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**Title:** Albuminuria-lowering effect of dapagliflozin alone and in combination with saxagliptin and effect of dapagliflozin and saxagliptin on glycaemic control in patients with type 2 diabetes and chronic kidney disease (DELIght): a randomised, double-blind, placebo-controlled trial.

**Citation:** The lancet. Diabetes & endocrinology; Jun 2019; vol. 7 (no. 6); p. 429-441

**Author(s):** Pollock, Carol; Stefánsson, Bergur; Reyner, Daniel; Rossing, Peter; Sjöström, C David; Wheeler, David C; Langkilde, Anna Maria; Heerspink, Hidde J L
Background: In patients with type 2 diabetes, intensive glucose control can be renoprotective and albuminuria-lowering treatments can slow the deterioration of kidney function. We assessed the albuminuria-lowering effect of the sodium-glucose co-transporter-2 inhibitor dapagliflozin with and without the dipeptidyl peptidase-4 inhibitor saxagliptin, and the effect of dapagliflozin-saxagliptin on glycaemic control in patients with type 2 diabetes and moderate-to-severe chronic kidney disease.

Methods: In this double-blind, placebo-controlled trial (DELIGHT), we enrolled patients at 116 research centres in Australia, Canada, Japan, South Korea, Mexico, South Africa, Spain, Taiwan, and the USA. We included patients with a known history of type 2 diabetes, increased albuminuria (urine albumin-to-creatinine ratio [UACR] 30-3500 mg/g), an estimated glomerular filtration rate of 25-75 mL/min per 1.73 m², and an HbA1c of 7.0-11.0% (53-97 mmol/mol), who had been receiving stable doses of angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker therapy and glucose-lowering treatment for at least 12 weeks. After a 4-week, single-blind placebo-run-in period, participants were randomly assigned (1:1:1; via an interactive voice-web response system) to receive dapagliflozin (10 mg) only, dapagliflozin (10 mg) and saxagliptin (2.5 mg), or placebo once-daily for 24 weeks. Primary endpoints were change from baseline in UACR (dapagliflozin and dapagliflozin-saxagliptin groups) and HbA1c (dapagliflozin-saxagliptin group) at week 24 in all randomly allocated patients with available data (full analysis set). This study is registered with ClinicalTrials.gov, number NCT02547935 and is completed.

Findings: The study took place between July 14, 2015, and May 18, 2018. 1187 patients were screened, of whom 461 were randomly assigned: 145 to the dapagliflozin group, 155 to the dapagliflozin-saxagliptin group, and 148 to the placebo group (13 patients were excluded because of data integrity issues). Dapagliflozin and dapagliflozin-saxagliptin reduced UACR versus placebo throughout the study period. At week 24, the difference (vs placebo; n=134 patients with available data) in mean UACR change from baseline was -21.0% (95% CI -34.1 to -5.2; p=0.011) for dapagliflozin (n=132) and -39.0% (-48.2 to -25.8; p<0.0001) for dapagliflozin-saxagliptin (n=139). HbA1c was reduced in the dapagliflozin-saxagliptin group (n=137) compared with the placebo group (n=118) at week 24 (-0.58 [-0.80 to -0.37; p<0.0001]). The numbers of patients with adverse events (79 [54%] in the dapagliflozin group, 104 [68%] in the dapagliflozin-saxagliptin group, and 81 [55%] in the placebo group) or serious adverse events (12 [8%], 12 [8%], and 16 [11%], respectively) were similar across groups. There were no new drug-related safety signals.

Interpretation: Dapagliflozin with or without saxagliptin, given in addition to angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker treatment, is a potentially attractive option to slow the progression of kidney disease in patients with type 2 diabetes and moderate-to-severe chronic kidney disease.

Funding: AstraZeneca.

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Title: Prevention and screening recommendations in type 2 diabetes: Review and critical appraisal of clinical practice guidelines.

Citation: Primary care diabetes; Jun 2019; vol. 13 (no. 3); p. 197-203

Author(s): Diab, Mohammad; Barhoosh, Huda A; Daoudi, Balqis; AlMukdad, Sawssan I; Zaghloul, Nancy Ha; Ashour, Mayar; Abdelrahman, Iman A; Paravattil, Bridget; Wilby, Kyle John

Abstract: The aim of this review was to identify and appraise guidelines reporting recommendations for the screening and prevention of type 2 diabetes. Five guidelines were included for analysis and all were endorsed by national or international organizations. All guidelines were recommended for practice with or without modifications for both prevention and screening. The overall appraisal scores ranged from 62.5 to 91.7 for prevention and 62.5-83.3 for screening. The highest scored domain was 'clarity of presentation' and the lowest was 'rigor of development'. Findings call for greater attention to rigor when formulating recommendations for prevention and screening of diabetes.

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Title: The Role of Health Literacy in Diabetes Knowledge, Self-Care, and Glycemic Control: a Meta-analysis.

Citation: Journal of general internal medicine; Jun 2019; vol. 34 (no. 6); p. 1007-1017
Background: Empirical evidence on how health literacy affects diabetes outcomes is inconsistent. The purpose of this meta-analysis was to quantitatively summarize the findings on the associations between health literacy and diabetes knowledge, self-care activities, and glycemic control as disease-related outcomes, with specific focus on the type of health literacy assessment.

Data Sources: Nine databases (MEDLINE, CINAHL, Communication and Mass Media Complete, PsychInfo, PsychArticles, Psychology and Behavioral Sciences Collection, ERIC, Sociology, Embase) were searched for peer-reviewed original research articles published until 31 March 2018.

Methods: Studies with type 1 and/or type 2 diabetes patients aged 18 or older, providing a calculable baseline effect size for functional health literacy and diabetes knowledge, self-care activities, or HbA1C were included.

Results: The meta-analysis includes 61 studies with a total of 18,905 patients. The majority were conducted in the USA, on type 2 diabetes patients, and used the S-TOFHLA as a performance-based or the BHLS as a perception-based measure of functional health literacy. Meta-analytic results show that all three outcomes are related to health literacy. Diabetes knowledge was best predicted by performance-based health literacy measures, self-care by self-report measures, and glycemic control equally by both types of health literacy assessment.

Discussion: Health literacy plays a substantial role in diabetes knowledge. Findings for the role of health literacy in self-care and glycemic control remain heterogeneous, partly due to the type of health literacy assessment (performance- vs. perception-based). This has implications for the use of health literacy measures in clinical settings and original research. This meta-analysis was limited to functional health literacy and, due to the paucity of studies, did not investigate the role of other dimensions including communicative and critical health literacy.

Title: Glycaemic control after treatment intensification in patients with type 2 diabetes uncontrolled on two or more non-insulin antidiabetic drugs in a real-world setting.

Citation: Diabetes, obesity & metabolism; Jun 2019; vol. 21 (no. 6); p. 1373-1380

Author(s): Canivell, Silvia; Mata-Cases, Manel; Real, Jordi; Franch-Nadal, Josep; Vlacho, Bogdan; Khunti, Kamlesh; Gratacòs, Mònica; Mauricio, Didac

Aim: To assess glycaemic control after treatment intensification in patients with type 2 diabetes uncontrolled on ≥2 non-insulin antidiabetic drugs (NIADS).

Methods: A retrospective cohort study, using electronic health records from the SIDIAP database (2010-2014), was conducted. Intensification was defined as the prescription of any new antidiabetic drug in patients treated with ≥2 NIADS and HbA1c >7%. The primary outcome was the absolute change in HbA1c 6-12 months after any intensification. Secondary analyses included the percentage of patients reaching HbA1c <7%, HbA1c <8%, and HbA1c 1%. High previous HbA1c was positively associated with the reduction of HbA1c >1% [odds ratio (OR) 2.13 (95% CI: 2.05-2.21)], but inversely associated with the attainment of HbA1c <7% [OR 0.64 (0.61-0.67)] or <8% [OR 0.63 (0.60-0.65)]. Older age, male gender, higher Charlson index, and short diabetes duration were associated with achievement of HbA1c <7%.

Conclusions: Despite intensification, most patients failed the glycaemic goal of HbA1c <7%. The reduction depended mainly on preintensification HbA1c values, with small differences between drugs.
Title: Comparable glycaemic control and hypoglycaemia in adults with type 2 diabetes after initiating insulin glargine 300 units/mL or insulin degludec: DELIVER Naïve D real-world study.

Citation: Diabetes, obesity & metabolism; May 2019

Author(s): Sullivan, Sean D; Nicholls, Charlie J; Gupta MTech, Rishab A; Meron, Arjun A; Wu, Jasmanda; Westerbacka, Jukka; Bosnyak, Zsolt; Frias, Juan P; Bailey, Timothy S

Aims: To compare glycaemic control, hypoglycaemia, and treatment discontinuation of insulin glargine 300 units/mL (Gla-300) and insulin degludec (IDeg) in a real-world study of insulin-naïve adults with type 2 diabetes (T2D).

Materials and Methods: DELIVER Naive D was a retrospective observational study that used electronic medical record data from the IBM® Watson Health™ Explorys database. Insulin-naïve adults with T2D who started Gla-300 or IDeg between March 2015 and September 2017 were identified. Patients were active in the system for ≥12 months before and ≥6 months after starting Gla-300 or IDeg and had glycated haemoglobin (HbA1c) measurements during 6-month baseline and 3- to 6-month follow-up. Outcomes were compared among 1:1 propensity score-matched cohorts.

Results: In the matched cohorts (n = 638 each), the mean age was 59 years, approximately 53% were male, and mean HbA1c was 9.67% (82 mmol/mol). Mean (SD) HbA1c decreases were comparable in the Gla-300 and IDeg cohorts (-1.67% [2.22] and -1.58% [2.20]; P = 0.51), as were HbA1c target attainment (<7% [53 mmol/mol]: 23.8% and 27.4%; P = 0.20; <8% [64 mmol/mol]: 55.0% and 57.1%; P = 0.63) and treatment discontinuation (29.2% and 32.6%; P = 0.14). Overall and inpatient/emergency department-associated hypoglycaemia incidences and event rates were similar in both cohorts, using fixed 6-month or variable on-treatment follow-up.

Conclusions: Among real-world insulin-naïve adults with T2D, initiation of Gla-300 or IDeg resulted in comparable improvements in glycaemic control and similar rates of hypoglycaemia. These real-world data complement and confirm a randomized trial and other real-world studies. This article is protected by copyright. All rights reserved.

Title: Sleep and Environmental Factors Affecting Glycemic Control in People with Type 2 Diabetes Mellitus.

Citation: Current diabetes reports; May 2019; vol. 19 (no. 7); p. 40

Author(s): Afroz-Hossain, Anika; Dawkins, Makeda; Myers, Alyson K

Purpose of Review: Sleep and environmental factors both impact glycemic control in persons with type 2 diabetes mellitus (T2DM). This narrative article aims to review research within the past 5 years, focusing on chronotype, light, noise, and neighborhood disparities in relation to sleep in people with T2DM.

Recent Findings: Sleep quality and duration have been shown to impact glycemic control in patients with T2DM. Later chronotype can lead to poorer glycemic control due to disruption of circadian rhythms. Light exposure also has similar effects, likely due to its inherent influence on sleep quality. Environmental determinants, were associated with lower T2DM incidence, and noise and air pollution were associated with increased risks for T2DM. Findings were mixed; while most studies found that later chronotype, light/noise exposure, and neighborhood disadvantages were associated with poorer glycemic control in patients with T2DM, other environmental factors, such as green space, were not significantly associated with diabetes outcomes.

Title: Cost-effectiveness of once-weekly semaglutide versus dulaglutide and lixisenatide in patients with type 2 diabetes with inadequate glycemic control in Sweden.

Citation: Journal of medical economics; May 2019 ; p. 1-9

Author(s): Ericsson, Åsa; Fridhammar, Adam
**Aims:** This analysis evaluated the cost-effectiveness of once-weekly semaglutide vs glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in patients with type 2 diabetes (T2D) uncontrolled on metformin or basal insulin in Sweden.

**Materials and Methods:** This cost-effectiveness analysis (CEA) was conducted using the Swedish Institute of Health Economics (IHE) Diabetes Cohort Model. Analyses were conducted from the Swedish societal perspective over a time horizon of 40 years. For patients uncontrolled on metformin, dulaglutide was the comparator, and data from the SUSTAIN 7 clinical trial was used. For patients uncontrolled on basal insulin, lixisenatide was chosen as the comparator and data was obtained from a network meta-analysis (NMA).

**Results:** The results show that, in patients with inadequate control on metformin, semaglutide 1.0 mg dominated (i.e. provided greater clinical benefit, and was less costly) dulaglutide 1.5 mg. In patients with inadequate control on basal insulin, semaglutide 1.0 mg dominated lixisenatide. The reduction in costs is largely driven by the reduction in complications seen with once-weekly semaglutide.

**Limitations and Conclusions:** It is likely that this analysis is conservative in estimating the cardiovascular (CV) cost benefits associated with treatment with once-weekly semaglutide. In patients inadequately controlled on basal insulin, the analyses vs lixisenatide were based on results from an NMA, as no head-to-head clinical trial has been conducted for this comparison. These CEA results show that once-weekly semaglutide is a cost-effective GLP-1 RA therapy for the treatment of T2D in patients inadequately controlled on metformin or basal insulin, addressing many current clinician, patient, and payer unmet needs in Sweden.

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**Title:** The Mediterranean Diet and 2-Year Change in Cognitive Function by Status of Type 2 Diabetes and Glycemic Control.

**Citation:** Diabetes care; May 2019

**Author(s):** Mattei, Josiemer; Bigorna, Sherman J; Sotos-Prieto, Mercedes; Scott, Tammy; Gao, Xiang; Tucker, Katherine L

**Objective:** To determine associations of a Mediterranean diet score (MeDS) with 2-year change in cognitive function by type 2 diabetes and glycemic control status and contrast it against other diet quality scores.

**Research Design and Methods:** We used data from the longitudinal Boston Puerto Rican Health Study (n = 913; 42.6% with type 2 diabetes at 2 years). Glycemic control at baseline was categorized as uncontrolled (hemoglobin A1c ≥7% [53 mmol/mol]) versus controlled. Two-year change in glycemic control was defined as stable/improved versus poor/declined. We defined MeDS, Healthy Eating Index, Alternate Healthy Eating Index, and Dietary Approaches to Stop Hypertension scores. Adjusted mixed linear models assessed 2-year change in global cognitive function z score, executive and memory function, and nine individual cognitive tests.

**Results:** Higher MeDS, but no other diet quality score, was associated with higher 2-year change in global cognitive function in adults with type 2 diabetes (β ± SE = 0.027 ± 0.011; P = 0.016) but not without (P = 0.80). Similar results were noted for Mini-Mental State Examination, word recognition, digit span, and clock drawing tests. Results remained consistent for individuals under glycemic control at baseline (0.062 ± 0.020; P = 0.004) and stable/improved over 2 years (0.053 ± 0.019; P = 0.007), but not for uncontrolled or poor/declined glycemic control. All diet quality scores were associated with higher 2-year memory function in adults without type 2 diabetes.

**Conclusions:** Both adhering to a Mediterranean diet and effectively managing type 2 diabetes may support optimal cognitive function. Healthy diets, in general, can help improve memory function among adults without type 2 diabetes.

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**Title:** Evaluation of the digital diabetes prevention programme pilot: uncontrolled mixed-methods study protocol.

**Citation:** BMJ open; May 2019; vol. 9 (no. 5); p. e025903
**Author(s):** Murray, Elizabeth; Daff, Kerry; Lavida, Anthi; Henley, William; Irwin, Jenny; Valabhji, Jonathan

**Introduction:** The prevalence of type 2 diabetes is rising steeply. National Health Service England (NHSE) is exploring the potential of a digital diabetes prevention programme (DDPP) and has commissioned a pilot with embedded evaluation.

**Methods And Analysis:** This study aims to determine whether, and if so, how, should NHSE implement a national DDPP, using a mixed-methods pretest and post-test design, underpinned by two theoretical frameworks: the Coventry, Aberdeen and London - Refined (CALO-RE) taxonomy of behavioural change techniques for the digital interventions and the Consolidated Framework for Implementation Research (CFIR) for implementation processes. In eight pilot areas across England, adults with non-diabetic hyperglycaemia (NDH) (glycated haemoglobin (HbA1c) 42-47 mmol/mol or fasting plasma glucose 5.5-6.9 mmol/L) and adults without NDH who are overweight (body mass index (BMI) >25 kg/m²) or obese (BMI >30 kg/m²) will be referred to one of five digitally delivered diabetes prevention interventions. The primary outcomes are reduction in HbA1c and weight (for people with NDH) and reduction in weight (for people who are overweight or obese) at 12 months. Secondary outcomes include use of the intervention, satisfaction, physical activity, patient activation and resources needed for successful implementation. Quantitative data will be collected at baseline, 6 months and 12 months by the digital intervention providers. Qualitative data will be collected through semistructured interviews with commissioners, providers, healthcare professionals and patients. Quantitative data will be analysed descriptively and using generalised linear models to determine whether changes in outcomes are associated with demographic and intervention factors. Qualitative data will be analysed using framework analysis, with data pertaining to implementation mapped onto the CFIR.

**Ethics and Dissemination:** The study has received ethical approval from the Public Health England Ethics and Research Governance Group (reference R&D 324). Dissemination will include a report to NHSE to inform future policy and publication in peer-reviewed journals.

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**Title:** Referral of patients to diabetes prevention programmes from community campaigns and general practices: mixed-method evaluation using the RE-AIM framework and Normalisation Process Theory.

**Citation:** BMC health services research; May 2019; vol. 19 (no. 1); p. 321

**Author(s):** Knowles, Sarah; Cotterill, Sarah; Coupe, Nia; Spence, Michael

**Background:** Each year around 5-10% of people with non-diabetic hyperglycaemia will develop type 2 diabetes mellitus. Diabetes prevention is a national and global public health concern. Diabetes Prevention Programmes, which seek to identify at-risk individuals and support entry to health improvement initiatives, recognise that enhanced identification and referral of at-risk individuals is required within primary care and beyond, through community-focused prevention approaches. We report an evaluation of a demonstrator site for the NHS Diabetes Prevention Programme in the UK, which piloted an enhanced Primary Care referral programme (sampling from patients identified as at-risk from general practice databases) and a Community identification programme (sampling from the general population through opportunistic identification in community locations) in an effort to maximise participation in prevention services.

**Methods:** We used mixed-methods evaluation to assess the impact of the two referral routes on participation in the Diabetes Prevention Programmes in line with the RE-AIM Framework (Reach, Effectiveness, Adoption, Implementation and Maintenance). Individual level patient data was descriptively analysed to assess identifications and eligible referrals made in each route. Semi-structured interviews conducted with referral staff and key stakeholders were analysed using thematic analysis and informed by Normalisation Process Theory.

**Results:** The nurse facilitated primary care referral route provided 88% of all referrals to the telephone DPP, compared to the community referral route which provided 5%, and the proportion joining the programme was higher among primary care referrals (45%) than community referrals (22%), and retention rates were higher (73% compared to 50%). The nurse-facilitated route integrated
more easily into existing clinical processes. The community programme was impeded by a lack of collaborative inter-agency working which obscured the intended focus on high-risk populations despite conversion rates (numbers identified at risk who entered prevention programmes) being highest in areas of high deprivation.

**Conclusion:** The study demonstrates the interaction of components, with effective Adoption and Implementation necessary to support Reach. The NPT analysis demonstrated the importance of consensus around not only the need for such programmes but agreement on how they can be delivered. Future programmes should support inter-agency communication and collaboration, and focus identification efforts on areas of high-risk.

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**Title:** Milk in the prevention and management of type 2 diabetes mellitus: the potential role of milk proteins.

**Citation:** Diabetes/metabolism research and reviews; May 2019; p. e3187

**Author(s):** Hidayat, Khemayanto; Du, Xuan; Shi, Bi-Min

**Abstract:** Globally, diabetes mellitus is not only considered a leading cause of mortality and morbidities but has also created a substantial economic burden. There is growing evidence that foods and their components can be implemented in the prevention and management of type 2 diabetes mellitus (T2DM). Increased dairy consumption has been linked to a lower risk of T2DM. The protective role of dairy foods in the development of T2DM is thought to be largely attributable to dairy nutrients, one of them being dairy protein. There is considerable evidence that milk proteins increase the postprandial insulin response and lower the postprandial blood glucose response in both healthy subjects and patients with T2DM. The exact mechanisms by which milk proteins lower postprandial glucose levels are yet to be established; however, the amino acids and bioactive peptides derived from milk proteins are thought to modify a physiological milieu, which includes delayed gastric emptying and the enhancement of incretin and insulin responses, consequently leading to lower postprandial glucose levels. The present review will focus on providing a clear presentation of the potential implementation of milk proteins as a dietary supplement in the prevention and management of T2DM by summarizing the relevant supporting evidence for this particular topic.

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**Title:** Effectiveness and Safety of Rivaroxaban and Warfarin for Prevention of Major Adverse Cardiovascular or Limb Events in Nonvalvular Atrial Fibrillation Patients with Type 2 Diabetes.

**Citation:** Diabetes, obesity & metabolism; May 2019

**Author(s):** Baker, William L; Beyer-Westendorf, Jan; Bunz, Thomas J; Eriksson, Daniel; Meinecke, Anna-Katharina; Sood, Nitesh A; Coleman, Craig I

**Aims:** To assess the effectiveness and safety of rivaroxaban versus warfarin for the prevention of major adverse cardiovascular events (MACE) and major adverse limb events (MALE) in nonvalvular atrial fibrillation (NVAF) patients' with type 2 diabetes (T2D).

**Materials and Methods:** Using MarketScan data from 1/2012-12/2017, we identified oral anticoagulant (OAC)-naïve NVAF patients with comorbid T2D and ≥12-months of insurance coverage prior to rivaroxaban or warfarin initiation. Differences in baseline covariates between cohorts were adjusted using inverse probability-of-treatment weights based on propensity scores (absolute standardized differences <0.1 achieved for all covariates after adjustment). Patients were followed until a MACE, MALE or major bleeding event, OAC discontinuation/switch, insurance disenrollment or end-of-data availability. Hazard ratios (HRs) and 95% confidence intervals (CIs) comparing the cohorts were calculated using Cox regression.

**Results:** We identified 10,700 rivaroxaban (24.1% received a reduced dose) and 13,946 warfarin users. Median (25, 75% range) age was 70 (62, 79) years, CHA2DS2-VASc score was 4 (3, 5) and duration of available follow-up was 1.4 (0.6, 2.7) years. Eleven percent of patients had peripheral artery disease, 5.1% had coronary artery disease, and 5.1% had a prior MALE, at baseline. Rivaroxaban was associated with a 25% (95%CI=4-41%) reduced risk of MACE and 63%
(95% CI = 35-79%) reduced risk of MALE compared to warfarin. Major bleeding risk did not significantly differ between cohorts (HR = 0.95).

**Conclusions:** Among NVAF patients with T2D treated in routine practice, rivaroxaban was associated with lower risks of both MACE and MALE versus warfarin; with no significant difference in major bleeding. This article is protected by copyright. All rights reserved.

**Title:** A 24-week, randomized, double-blind, active-controlled clinical trial comparing bexagliflozin to sitagliptin as an adjunct to metformin for the treatment of type 2 diabetes in adults.

**Citation:** Diabetes, obesity & metabolism; Jun 2019

**Author(s):** Halvorsen, Yuan-Di; Lock, J Paul; Zhou, Wenjiong; Zhu, Fang; Freeman, Mason W

**Aim:** To compare the relative safety and effectiveness of bexagliflozin and sitagliptin as adjuncts to metformin for the treatment of type 2 diabetes.

**Methods:** Participants (n = 386) were randomized to receive bexagliflozin (20 mg) or sitagliptin (100 mg) in addition to their existing doses of metformin. The primary endpoint was the noninferiority of bexagliflozin to sitagliptin for change in HbA1c from baseline to week 24. Changes from baseline to week 24 in fasting plasma glucose (FPG), body mass (in subjects with baseline BMI ≥ 25 kg m⁻²) and systolic blood pressure (SBP) were secondary endpoints.

**Results:** The mean change from baseline to week 24 in HbA1c was -0.74 (95% CI -0.86%, -0.62%) in the bexagliflozin arm and -0.82% (95% CI -0.93%, -0.71%) in the sitagliptin arm, establishing non-inferiority. The changes from baseline FPG, body mass and SBP were -1.82 mmol/L, -3.35 kg and -4.23 mm Hg in the bexagliflozin arm and -1.45 mmol/L, -0.81 kg and -1.90 mm Hg in the sitagliptin arm. These differences were significant for the first two measures (one-sided p = 0.0123, p < 0.0001 and p = 0.0276, respectively.) Adverse events were experienced by 47.1% of subjects in the bexagliflozin arm and 56.0% of subjects taking sitagliptin. Serious adverse events affected 3.7% of subjects in the bexagliflozin arm and 2.1% of subjects in the sitagliptin arm.

**Conclusions:** Bexagliflozin was non-inferior to sitagliptin and provided benefits over sitagliptin in FPG and body mass. Adverse event incidences in the two arms were similar. This article is protected by copyright. All rights reserved.

**Title:** Dietary patterns and management of type 2 diabetes: A systematic review of randomised clinical trials.

**Citation:** Nutrition, metabolism, and cardiovascular diseases : NMCD; Jun 2019; vol. 29 (no. 6); p. 531-543

**Author(s):** Papamichou, D; Panagiotakos, D B; Itsiopoulos, C

**Background and Aim:** The aim of the present review is to examine evidence from published studies on the effectiveness of six or more months of low carbohydrate, macrobiotic, vegan, vegetarian, Mediterranean and intermittent fasting (IF) diets compared to low fat diets on diabetes control and management.

**Methods and Results:** In accordance with PRISMA guidelines, Cochrane CENTRAL, PubMed and Scopus databases were systematically searched for relevant studies. Twenty randomised controlled trials (RCTs) > 6 months that investigated the effectiveness of various dietary patterns on type 2 diabetes mellitus (T2DM) were included. Risk of bias was assessed using the Cochrane tool. There were no significant differences in glycemic control, weight and lipids for the majority of low carbohydrate diets (LCDs) compared to low fat diets (LFDs). Four out of fifteen LCD interventions showed better glycemic control while weight loss was greater in one study. The Mediterranean dietary pattern demonstrated greater reduction in body weight and HbA1c levels and delayed requirement for diabetes medications. The vegan and macrobiotic diet demonstrated improved glycemic control, while the vegetarian diet showed greater body weight reduction and insulin sensitivity.
Conclusions: Although more long-term intervention trials are required, mounting evidence supports the view that vegan, vegetarian and Mediterranean dietary patterns should be implemented in public health strategies, in order to better control glycemic markers in individuals with T2DM.

Title: Filling the intervention gap: service evaluation of an intensive nonsurgical weight management programme for severe and complex obesity.

Citation: Journal of human nutrition and dietetics : the official journal of the British Dietetic Association; Jun 2019; vol. 32 (no. 3); p. 329-337

Author(s): McCombie, L; Brosnahan, N; Ross, H; Bell-Higgs, A; Govan, L; Lean, M E J

Background: Weight management including formula total diet replacement (TDR) is emerging as an effective intervention for severe and complex obesity, particularly with respect to type 2 diabetes (T2DM). However, no prospective audit and service evaluation of such programmes have been reported.

Methods: Following initial feasibility piloting, the Counterweight-Plus programme was commissioned across a variety of healthcare providers. The programme includes: Screening, TDR (formula low energy diet), food reintroduction and weight loss maintenance, all delivered by staff with 8 h of training, in-service mentoring, ongoing specialist support and access to medical consultant expertise. Anonymised data are returned centrally for clinical evaluation.

Results: Up to December 2016, 288 patients commenced the programme. Mean (SD) baseline characteristics were: age 47.5 (12.7) years, weight 128.0 (32.0) kg, body mass index 45.7 (10.1) kg m\(^{-2}\), n = 76 (26.5%) were male and n = 99 (34.5%) had T2DM. On an intention-to-treat (ITT) basis, a loss of ≥15 kg at 12 months was achieved by 48 patients, representing 22.1% of all who started and 40% of those who maintained engagement. For complete cases, mean (95% confidence interval) weight loss was 13.3 (12.1-14.4) kg at 3 months, 16.0 (14.4-17.6) kg at 6 months and 14.2 (12.1-16.3) kg at 12 months (all P < 0.001), with losses to follow-up of 10.8%, 29.3% and 44.2%, respectively. Mean loss at 12 months by ITT analyses was: single imputation -10.5 (9.5) kg, last observation carried forward -10.9 (11.6) kg and baseline observation carried forward -7.9 (11.1) kg. The presence of diabetes had no significant impact on weight change outcomes.

Conclusions: This nonsurgical approach is effective for many individuals with severe and complex obesity, representing an option before considering surgery. The results are equally effective in terms of weight loss for people with T2DM.

Title: Timing of GLP-1 Receptor Agonist Initiation for Treatment of Type 2 Diabetes in the UK.

Citation: Drugs in R&D; Jun 2019; vol. 19 (no. 2); p. 213-225

Author(s): Boye, Kristina S; Stein, Dara; Matza, Louis S; Jordan, Jessica; Yu, Ren; Norrbacka, Kirsi; Hassan, Syed Wasi; García-Pérez, Luis-Emilio

Introduction: Patients with type 2 diabetes mellitus (T2DM) who fail to meet glycaemic control are at increased risk of diabetes complications. For patients who cannot maintain glycaemic control with oral medication, one recommended option is to add an injectable glucagon-like peptide-1 receptor agonist (GLP-1 RA) to their treatment regimen. The purpose of this study was to examine time to treatment intensification with GLP-1 RAs, including the duration of time that patients did not maintain glycaemic control with oral medication.

Methods: This was a medical record review conducted in the UK via a physician survey. Patients eligible to have their records reviewed were required to be ≥ 18 years of age, have a confirmed T2DM diagnosis, and have initiated GLP-1 RA treatment for T2DM in the past 6 months. All glycated haemoglobin (HbA1c) values within 5 years prior to GLP-1 RA initiation were collected.

Results: A total of 113 physicians contributed data for 1096 patients (mean age at the time of GLP-1 RA initiation was 54.9 years, 55.4% were male, and 71.4% were White). Median time from T2DM diagnosis to GLP-1 RA initiation was 6.1 years. Median consecutive time patients taking oral
regimens were not under glycaemic control (HbA1c > 7.0%) prior to GLP-1 RA initiation was 13.5 months. Patients treated by general practitioners (GPs) had a significantly longer duration of time with insufficient glycaemic control prior to GLP-1 RA initiation compared with patients treated by diabetes specialists (median time for specialists was 11.0 months vs. 17.0 months for GPs; p = 0.038).

**Conclusions:** Results suggest that treatment intensification is often delayed despite consistently poor glycaemic control for more than 12 months, contrary to treatment guideline recommendations. Findings from this study highlight that some T2DM patients may benefit from more rapid treatment intensification, which could improve glycaemic control and reduce the risk for many short- and long-term health complications.

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**Title:** Digital health technology and mobile devices for the management of diabetes mellitus: state of the art.

**Citation:** Diabetologia; Jun 2019; vol. 62 (no. 6); p. 877-887

**Author(s):** Shan, Rongzi; Sarkar, Sudipa; Martin, Seth S

**Abstract:** Diabetes mellitus is a disease that can be difficult to manage and requires high levels of health literacy and numeracy, self-monitoring and frequent contact with clinicians. If not optimally controlled, diabetes can lead to kidney failure, blindness and cardiovascular complications, which, in turn, contribute to increasing healthcare costs. Although not yet widely used, mobile health (mHealth) tools have enhanced diabetes management and prevention and are likely to play an increasing role with the growth of smartphone ownership and medical device innovations. Recent mHealth interventions targeting type 1 and type 2 diabetes are diverse in their goals and components, and include insulin management applications, wearable blood glucose meters, automated text messages, health diaries and virtual health coaching. In this paper, we review the modalities and components of various impactful interventions for insulin management, diabetes education, self-management and prevention. More work is needed to investigate how individual demographic, socioeconomic, behavioural and clinical characteristics contribute to patient engagement and the efficacy of mHealth tools for diabetes.

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**Title:** Exploring organizational support for the provision of structured self-management education for people with Type 2 diabetes: findings from a qualitative study.

**Citation:** Diabetic medicine : a journal of the British Diabetic Association; Jun 2019; vol. 36 (no. 6); p. 761-770

**Author(s):** Carey, M E; Agarwal, S; Horne, R; Davies, M; Slevin, M; Coates, V

**Aim:** To explore the organizational context in which Type 2 diabetes structured group education is provided.

**Methods:** Four Clinical Commissioning Groups in England providing Type 2 diabetes structured self-management education participated in a qualitative study exploring the context for provision of that education. Using UK National Diabetes Audit returns, two Clinical Commissioning Groups were selected that had non-attendance rates of ≤25%, and two that had non-attendance rates of ≥50%. Between May 2016 and August 2017, 20 interviews were conducted with Clinical Commissioning Group staff including: commissioners, healthcare professionals, managers, general practitioners and diabetes educators. Data gathering was prolonged as it proved challenging to engage with healthcare staff as a result of frequent local restructuring and service disruption.

**Results:** Local audits revealed discrepancies in basic data such as referral and attendance numbers compared with national audit data. There was a commonality in the themes identified from interviews: diabetes education was rarely embedded in service structure; where education uptake was poor, a lack of central support to delivery teams was noticeable; and where education uptake was positive, delivery teams were actively engaged, sometimes relying on enthusiastic individuals. Both situations put the local sustainability of diabetes education at risk.
Conclusions: There appears to be a link between attendance rates and organizational issues, therefore, when considering how to increase attendance rates, the state of the diabetes education infrastructure should be reviewed. Good uptake of diabetes education can be too reliant on the enthusiastic commitment of small teams or individuals delivering the education.

Title: Superior efficacy of insulin degludec/liraglutide versus insulin glargine U100 as add-on to sodium-glucose co-transporter-2 inhibitor therapy: A randomized clinical trial in people with uncontrolled type 2 diabetes.

Citation: Diabetes, obesity & metabolism; Jun 2019; vol. 21 (no. 6); p. 1399-1408
Author(s): Philis-Tsimikas, Athena; Billings, Liana K; Busch, Robert; Portillo, Cristobal Morales; Sahay, Rakesh; Halladin, Natalie; Eggert, Sarah; Begtrup, Kamilla; Harris, Stewart

Aim: To investigate the efficacy and safety of insulin degludec/liraglutide (IDegLira) versus insulin glargine 100 units/mL (IGlar U100) as add-on to sodium-glucose co-transporter-2 (SGLT2) inhibitor therapy.

Materials And Methods: In this 26-week, phase IIIb, open-label, parallel-group, treat-to-target trial, conducted at 74 sites in 11 countries, insulin-naïve people aged ≥18 years with glycated haemoglobin (HbA1c) 53-97 mmol/mol (7.0-11.0%), body mass index 20-40 kg/m² and inadequately controlled type 2 diabetes (T2D) on SGLT2 inhibitor ± oral antidiabetic drugs were randomized 1:1 to once-daily IDegLira or IGlar U100, both as add-on to existing therapy. The primary endpoint was change in HbA1c from baseline to week 26.

Results: A total of 210 participants were randomized to each treatment arm. Mean HbA1c reductions were 21 mmol/mol (1.9%-points) with IDegLira and 18 mmol/mol (1.7%-points) with IGlar U100; confirming non-inferiority (P < 0.0001) and superiority of IDegLira (difference in HbA1c change -3.90 mmol/mol; 95% confidence interval [CI] -5.45; -2.35 (-0.36%-points; 95% CI -0.50, -0.21)). Superiority for IDegLira over IGlar U100 was also confirmed for: body weight (difference -1.92 kg; 95% CI -2.64, -1.19); severe or blood-glucose-confirmed symptomatic hypoglycaemia (rate ratio 0.42; 95% CI 0.23, 0.75); total daily insulin dose (difference -15.37 U; 95% CI -19.60, -11.13). The overall treatment-emergent adverse event rate was higher with IDegLira as a result of higher increased lipase and nausea rates.

Conclusions: The favourable safety and efficacy profile of IDegLira in people with uncontrolled T2D on SGLT2 inhibitors, and lower weight gain and hypoglycaemia risk versus IGlar U100, suggest that clinicians should consider IDegLira initiation in this population.

Title: Relative contribution of basal and postprandial hyperglycaemia stratified by HbA1c categories before and after treatment intensification with dulaglutide.

Citation: Diabetes, obesity & metabolism; Jun 2019; vol. 21 (no. 6); p. 1365-1372
Author(s): Umpierrez, Guillermo; Pantalone, Kevin M; Atisso, Charles M; Landó, Laura Fernández; Patel, Hiren

Aim: To assess the effect of dulaglutide on the relative contribution of basal hyperglycaemia (BHG) and postprandial hyperglycaemia (PPHG) to overall hyperglycaemia across HbA1c categories in patients with type 2 diabetes.

Methods: Data from five phase 3 studies (N = 673) were pooled to assess the change in relative contributions of BHG and PPHG to overall hyperglycaemia across different HbA1c categories after 6 months of treatment intensification with dulaglutide 1.5 mg as monotherapy or with 1 or 2 oral medication(s) in patients with type 2 diabetes. BHG and PPHG were calculated using the area under the curve (AUC) of 7-point self-monitored plasma glucose concentration profiles. As a secondary objective, relative contribution of BHG and PPHG for dulaglutide versus liraglutide, exenatide BID and insulin glargine was assessed by individual studies at 6 months.
**Results:** In pooled data, after 6 months of treatment intensification with dulaglutide 1.5 mg, there was a significant reduction from baseline in overall hyperglycaemia (AUCoverall) [(mean ± SE) - 466.31 ± 18.32 mg*h/dL (P < 0.001)], BHG (AUCbasal) [(mean ± SE) - 371.46 ± 16.36 mg*h/dL (P < 0.001)] and PPHG (AUCpostprandial) [(mean ± SE) - 94.84 ± 7.97 mg*h/dL (P < 0.001)]. At baseline, relative contributions of BHG increased and PPHG decreased with increasing HbA1c levels. This pattern was maintained at 6 months, even as overall glycaemia improved with decreasing HbA1c values.

**Conclusions:** In patients with type 2 diabetes, dulaglutide reduces HbA1c by lowering both basal and postprandial hyperglycaemia across various HbA1c levels.

**Title:** Heart failure in the patient with diabetes: Epidemiology, aetiology, prognosis, therapy and the effect of glucose-lowering medications.

**Citation:** Diabetes, obesity & metabolism; Jun 2019; vol. 21 (no. 6); p. 1277-1290

**Author(s):** Bell, David S H; Goncaolves, Edison

**Abstract:** In people with type 2 diabetes the frequency of heart failure (HF) is increased and mortality from HF is higher than with non-diabetic HF. The increased frequency of HF is attributable to the cardiotoxic tetrad of ischaemic heart disease, left ventricular hypertrophy, diabetic cardiomyopathy and an extracellular volume expansion resistant to atrial natriuretic peptides. Activation of the renin-angiotensin-aldosterone system and sympathetic nervous systems results in cardiac remodelling, which worsens cardiac function. Reversal of remodelling can be achieved, and cardiac function improved in people with HF with reduced ejection fraction (HFrEF) by treatment with angiotensin-converting enzyme inhibitors and β-blockers. However, with HF with preserved ejection fraction (HFpEF), only therapy for the underlying risk factors helps. Blockers of mineralocorticoid receptors may be beneficial in both HFrEF and HFpEF. Glucose-lowering drugs can have a negative effect (insulin, sulphonylureas, dipeptidyl peptidase-4 inhibitors and thiazolidinediones), a neutral effect (α-glucosidase inhibitors and glucagon-like peptide-1 receptor agonists) or a positive effect (sodium-glucose co-transporter-2 inhibitors and metformin).

**Title:** Effectiveness and Tolerability of Vildagliptin and the Single Pill Combination of Vildagliptin and Metformin in "Real-World" Management of Type 2 Diabetes Mellitus: The G-FORCE Study.

**Citation:** Diabetes therapy : research, treatment and education of diabetes and related disorders; Jun 2019; vol. 10 (no. 3); p. 965-979

**Author(s):** Van Gaal, Luc; Hermans, Michel P; Daci, Evis; Denhaerynck, Kris; De Meester, Lut; MacDonald, Karen; Abraham, Ivo; Vancayzeele, Stefaan; Maris, Michael

**Introduction:** Randomized clinical trials showed that vildagliptin is well tolerated and leads to clinically meaningful decreases in glycated hemoglobin (HbA1c) and fasting plasma glucose (FPG) both in monotherapy and as add-on therapy in inadequately controlled type 2 diabetes mellitus (T2DM) patients. Nevertheless, there is an increased interest for real-life studies to confirm the clinical trial findings in the setting of a daily clinical practice. The aim of this study was to evaluate the effectiveness and tolerability of vildagliptin in a real-life clinical setting and to explore factors determining drug adherence and T2DM management.

**Methods:** G-FORCE was a prospective, observational, open-label, multi-center study in which T2DM patients were prescribed de novo vildagliptin. Clinical effectiveness was determined by changes in HbA1c and FPG and by the proportion of patients reaching glycemic goal. Data were collected at baseline, after 105 ± 15 days and after 180 ± 15 days.

**Results:** A total of 1230 patients were included in this analysis. Mean age was 63.9 ± 10.8 years, and mean HbA1c and FPG levels were 8.2 ± 1.3% and 171.0 ± 53.3 mg/dL, respectively. At 180 days of treatment, HbA1c and FPG levels decreased to 7.2 ± 1.0% and 141.1 ± 44.0 mg/dL, respectively,
while the proportion of patients reaching HbA1c and FPG goals rose from 8.6 to 44.6% and from 14.2 to 42.8%, respectively.

**Conclusion:** In this real-world study, vildagliptin was an effective and safe treatment for T2DM patients already treated with metformin, while the single pill combination of vildagliptin and metformin provides a convenient alternative while ensuring comparable effectiveness and tolerability.

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**Title:** Management of hyperglycaemia in persons with non-insulin-dependent type 2 diabetes mellitus who are started on systemic glucocorticoid therapy: a systematic review.

**Citation:** BMJ open; Jun 2019; vol. 9 (no. 5); p. e028914

**Author(s):** Tatalovic, Milos; Lehmann, Roger; Cheetham, Marcus; Nowak, Albina; Battegay, Edouard; Rampini, Silvana K

**Objectives:** What is the most effective pharmacological intervention for glycaemic control in known type 2 diabetes mellitus (DM) without prior insulin treatment and newly started on systemic glucocorticoid therapy?

**Design:** We conducted a systematic literature review.

**Data Sources:** We searched MEDLINE, Embase and Cochrane Library databases and Google for articles from 2002 to July 2018.

**Eligibility Criteria:** We combined search terms relating to DM (patients, >16 years of age), systemic glucocorticoids, glycaemic control, randomised controlled trials (RCTs) and observational studies.

**Data Extraction and Synthesis:** We screened and evaluated articles, extracted data and assessed risk of bias and quality of evidence according to Grading of Recommendations Assessment, Development and Evaluation guidelines.

**Results:** Eight of 2365 articles met full eligibility criteria. Basal-bolus insulin (BBI) strategy for patients under systemic glucocorticoid therapy was comparatively effective but provided insufficient glucose control, depending on time of day. BBI strategy with long-acting insulin and neutral protamin Hagedorn as basal insulin provided similar overall glycaemic control. Addition of various insulin strategies to standard BBI delivered mixed results. Intermediate-acting insulin (IMI) as additional insulin conferred no clear benefits, and glycaemic control with sliding scale insulin was inferior to BBI or IMI. No studies addressed whether anticipatory or compensatory insulin adjustments are better for glycaemic control.

**Conclusion:** The lack of suitably designed RCTs and observational studies, heterogeneity of interventions, target glucose levels and glucose monitoring, poor control of DM subgroups and low to moderate quality of evidence render identification of optimal pharmacological interventions for glycaemic control and insulin management difficult. Even findings on the widely recommended BBI regimen as intensive insulin therapy for patients with DM on glucocorticoids are inconclusive. High-quality evidence from studies with well-defined DM phenotypes, settings and treatment approaches is needed to determine optimal pharmacological intervention for glycaemic control.

**Prospero Registration Number:** CRD42015024739.

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**Title:** Triple Therapy With Low-Dose Dapagliflozin Plus Saxagliptin Versus Dual Therapy With Each Monocomponent, All Added to Metformin, in Uncontrolled Type 2 Diabetes.

**Citation:** Diabetes, obesity & metabolism; May 2019

**Author(s):** Rosenstock, Julio; Perl, Shira; Johnsson, Eva; García-Sánchez, Ricardo; Jacob, Stephan

**Aims:** To evaluate efficacy and safety of triple therapy with low-dose dapagliflozin plus saxagliptin added to metformin in uncontrolled type 2 diabetes.

**Materials And Methods:** This 24-week, double-blind trial (NCT02681094), randomized 883 patients (HbA1c 7.5-10.0%) on metformin ≥1500 mg/day to add-on dapagliflozin 5 mg/day plus saxagliptin 5
mg/day or to add-on of either monocomponent. The primary end point was change in HbA1c from baseline.

Results: Baseline mean ± standard deviation patient characteristics were: age, 56.7 ± 10.5 years; HbA1c, 8.2 ± 0.9%; diabetes duration, 7.6 ± 6.1 years. Triple therapy significantly decreased HbA1c versus dual therapy (-1.03% vs. -0.63% [dapagliflozin] vs. -0.69% [saxagliptin]; P < 0.0001). More patients achieved HbA1c <7.0% with triple versus dual therapy (41.6% vs. 21.8% [dapagliflozin; P < 0.0001] vs. 29.8% [saxagliptin; P = 0.0018]). Triple therapy significantly decreased fasting plasma glucose (-28 mg/dL vs. -20 mg/dL [dapagliflozin; P = 0.0135] vs. -13 mg/dL [saxagliptin; P < 0.0001]) and body weight (-2.0 kg vs. -0.4 kg [saxagliptin; P < 0.0001]) and β-hydroxybutyrate levels were lower than with dapagliflozin plus metformin (mean difference, -0.51; P = 0.0009). Urinary tract/genital infections and hypoglycaemia occurred in <5.0% and 5.8% of patients, respectively, with triple therapy.

Conclusions: Triple therapy with once-daily dapagliflozin 5 mg, saxagliptin 5 mg and metformin significantly improved glycemic control versus dual therapy with either agent added to metformin in uncontrolled type 2 diabetes and was generally well tolerated. This article is protected by copyright. All rights reserved.

### Title: Effects of Sitagliptin on Lipid Profile in Patients With Type 2 Diabetes Mellitus After 7 Years of Therapy.

**Citation:** Journal of clinical pharmacology; May 2019

**Author(s):** Derosa, Giuseppe; Tritto, Isabella; Romano, Davide; D'Angelo, Angela; Catena, Gabriele; Maffioli, Pamela

**Abstract:** The aim of this study was to investigate whether the effects of sitagliptin on lipid profile were maintained even after 7 years of treatment. We treated 591 patients who had not been well controlled by current therapy with the addition of sitagliptin 100 mg/d. Data were compared with those of 612 patients treated with sulfonylureas plus metformin, pioglitazone plus metformin, and pioglitazone plus sulfonylureas. We observed that, compared with patients treated with sulfonylureas plus metformin, patients receiving sitagliptin in addition to metformin experienced a greater decrease of total cholesterol and low-density lipoprotein cholesterol (LDL-C) compared with baseline and with sulfonylureas plus metformin. Compared with patients treated with metformin plus pioglitazone, sitagliptin resulted in a greater reduction of total cholesterol and LDL-C relative to baseline and to metformin plus pioglitazone. We also observed a higher increase of high-density lipoprotein cholesterol (HDL-C) after sitagliptin had been added to pioglitazone, both compared with baseline and to the competitor. Compared with patients treated with pioglitazone plus sulfonylureas, the combination of sitagliptin and sulfonylureas was more effective in reducing LDL-C and in increasing HDL-C. High-sensitivity C-reactive protein was decreased by all pharmacological combinations. We can conclude that the addition of sitagliptin led to a better and more durable improvement of lipid profile compared with sulfonylureas or thiazolidinediones.

### Title: The Effects of Popular Diets on Type 2 Diabetes Management.

**Citation:** Diabetes/metabolism research and reviews; May 2019 ; p. e3188

**Author(s):** Chester, Brittannie; Babu, Jeganathan Ramesh; Greene, Michael W; Geetha, Thangiah

**Abstract:** Type 2 diabetes can be managed with the use of diabetes self-management skills. Diet and exercise are essential segments of the lifestyle changes necessary for diabetes management. However, diet recommendations can be complicated in a world full of different diets. This review aims to evaluate the evidence on the effects of three popular diets geared towards diabetes management: low carbohydrate and the ketogenic diet, vegan diet, and the Mediterranean diet. While all three diets have been shown to assist in improving glycemic control and weight loss, patient adherence, acceptability, and long-term manageability play essential roles in the efficacy of each diet.
Incident type 2 diabetes in obstructive sleep apnea and effect of continuous positive airway pressure treatment: A retrospective clinic cohort study.

Citation: Chest; May 2019  
Author(s): Xu, Pei Hang; Hui, Christopher K M; Lui, Macy M S; Lam, David C L; Fong, Daniel Y T; Ip, Mary S M

Background: The relationship between OSA and glucose metabolism remains controversial. This retrospective study investigated the relationship between OSA and incident type 2 diabetes (T2D) in a clinic cohort of Chinese adults in Hong Kong, and the effect of long-term continuous positive airway pressure (CPAP) treatment.

Methods: Data for diagnosis of incident T2D and CPAP usage were obtained from the territory-wide electronic health administration system and records of protocolized evaluation of CPAP adherence at the sleep clinic. The relationship between baseline OSA and incident T2D and the effect of CPAP therapy were examined by Cox regression models. Risk of incident T2D over the continuum of apnea-hypopnea index (AHI) was examined with cubic spline analysis.

Results: Of 1206 subjects with overnight sleep studies and clinical assessment in 2006-2013, 152 developed diabetes (median follow-up 7.3 years). In fully adjusted models, untreated moderate or severe OSA patients had higher risk of developing diabetes, hazards ratio 2.01 (95% CI, 1.06-3.81) and 2.62 (95% CI, 1.40-4.93) respectively, with a trend to plateau in those with severe OSA. No interaction was demonstrated between OSA and obesity. Regular CPAP use, which was attained in about one-third of subjects with moderate-severe OSA, was associated with reduction of diabetes incidence from 3.41 to 1.61 per 100 person-years, and of adjusted hazard risk to that of non-OSA.

Conclusions: While OSA severity independently predicted incident diabetes, regular long-term CPAP use was associated with reduced risk of incident T2D, after adjustment for various baseline metabolic risk factors and subsequent body weight change.


Citation: Diabetes research and clinical practice; May 2019; vol. 152; p. 119-124  
Author(s): Koc, E Meltem; Aksoy, Hilal; Ayhan Başer, Duygu; Baydar Artantaş, Aylin; Kahveci, Rabia

Aims: Diabetes mellitus is one of the most significant global health emergencies of the 21st century. Every year, an increasing number of people succumb to the condition and therefore suffer life-changing complications. So management of this disease has an important role to prevent complications. In this study, our objective is to assess the quality of guidelines related to the significant public health problem diabetes that have been developed by international and national organizations using the AGREE II tool.

Methods: This observational study assesses the quality of clinical practice guidelines used in the management of diabetes with AGREE II tool. Statistical analysis was performed using the SPSS 20 program package.

Results: The overall quality score of the guidelines ranges between 3 and 6.25. While NICE's guidelines scored the highest, the guidelines of the National Diabetes Foundation scored the lowest.

Conclusion: More comprehensive studies are needed for assessing the quality of guidelines in every subject.

Title: Neprilysin inhibition: a new therapeutic option for type 2 diabetes?

Citation: Diabetologia; May 2019  
Author(s): Esser, Nathalie; Zraika, Sakeneh
Abstract: Neprilysin is a widely expressed peptidase with broad substrate specificity that preferentially hydrolyses oligopeptide substrates, many of which regulate the cardiovascular, nervous and immune systems. Emerging evidence suggests that neprilysin also hydrolyses peptides that play an important role in glucose metabolism. In recent studies in humans, a dual angiotensin receptor-neprilysin inhibitor (ARNi) improved glycaemic control and insulin sensitivity in individuals with type 2 diabetes and/or obesity. Moreover, preclinical studies have also reported that neprilysin inhibition, alone or in combination with renin-angiotensin system blockers, elicits beneficial effects on glucose homeostasis. Since neprilysin inhibitors have been approved for the treatment of heart failure, their repurposing for treating type 2 diabetes would provide a novel therapeutic strategy. In this review, we evaluate existing evidence from preclinical and clinical studies in which neprilysin is deleted/inhibited, we highlight potential mechanisms underlying the beneficial glycaemic effects of neprilysin inhibition, and discuss possible deleterious effects that may limit the efficacy and safety of neprilysin inhibitors in the clinic. We also review the favourable impact neprilysin inhibition can have on diabetic complications, in addition to glucose control. Finally, we conclude that neprilysin inhibitors may be a useful therapeutic option for treating type 2 diabetes; however, their combination with angiotensin II receptor blockers is needed to circumvent deleterious consequences of neprilysin inhibition alone.

Sources Used:
The following databases are used in the creation of this bulletin: BNI, CINAHL, EMBASE and Medline.

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