

**Metabolic and molecular effects of a high-protein diet in subjects with type 2 diabetes.**

Markova M et al. Abstract 701: Presented at: EASD 2015; Sept. 14-18, 2015; Stockholm

This study from Germany compared the effects of two high-protein diets (both animal protein-based and the other was plant protein-based) with the same number of calories on metabolic functioning and liver fat. Their data indicated that high-protein diets may be favourable for some patients with type 2 diabetes involving 37 patients with type 2 diabetes (24 men and 13 women). They examined metabolic markers, liver fat content and signaling pathways in white blood cells and adipose tissue.

Patients' mean age was 65 years, mean BMI was 30 and mean HbA1c was 7.0%. All of them were randomly assigned to the high-animal protein (meat and dairy foods) or the high-plant protein diet for 6 weeks, both diets consisting of 30% protein, 40% carbohydrates and 30% fat.

Before and after the diet intervention magnetic resonance imaging, hyperinsulinemic euglycemic clamps and meal tolerance tests were done. They also collected blood and subcutaneous adipose tissue samples.

The liver enzyme tests improved after intervention in both groups, and both liver fat and HbA1c were reduced in all participants. Insulin sensitivity improved only in the animal-protein group, but in the plant-protein group, there was a significant reduction in plasma creatinine and an improvement in general kidney function, as measured by glomerular filtration rate, which was not found in the animal-protein group. Specifically, in the plant-protein group, there were significant reductions in plasma creatinine ( $-7.79$   $\mu\text{mol/L}$ ) and improvement in the glomerular filtration rate, which went from 75.95 to 88.15 mL/min/1.73 m<sup>2</sup>.

**Editor's Comment**

**A high-protein diet may be beneficial for patients with type 2 diabetes. Whether of animal or plant protein in origin, a 6-week high-protein diet may lead to an improvement in glucose metabolism and a decrease in liver fat content in patients with type 2 diabetes without any adverse effects on kidney. Rather plant-protein diet may even improve kidney function.**

**Evaluating the Effects of Metformin Use on Height in Children and Adolescents**

A Meta-analysis of Randomized Clinical Trials. Nicholas Kuzik, Étienne Myette-Côté, Valerie Carson, Linda Slater, ; Normand G. Boulé, JAMA Pediatr. Published online September 28, 2015. doi:10.1001/jamapediatrics.2015.2186

Metformin hydrochloride use is increasing in children and adolescents. Previous meta-analyses have identified a large variability in the effects of metformin use on body mass index changes but have not considered height changes as a confounder. This study conducted a systematic review and meta-analysis of the effects of metformin use on height in children and adolescents. Randomized clinical trials examining the effects of metformin use on height of participants younger than 19 years were considered for this analysis.

Ten studies were included, with a total of 562 participants, 330 (58.7%) of whom were female. The mean age within the studies ranged from 7.9 to 16.1 years, with a high variability in most studies. The duration of metformin

interventions lasted from 3 to 48 months. Overall, height changes were not significantly different between the metformin and control groups. However, stratified analyses according to the cumulative metformin dose (in milligrams per day times the number of days of treatment) showed a greater increase in height with metformin use in the 5 studies providing the largest cumulative metformin doses (weighted mean difference, 1.0; 95% CI, 0.0 to 2.0 cm) but not in the 5 studies providing the lowest doses (weighted mean difference, -0.1; 95% CI, -0.7 to 1.0 cm) compared with the control group.

#### Editor's Comment

**Apparently the evidence suggests a dose-response relationship between metformin use and increases in height in children and adolescents when compared with a control group. While an approximate 1-cm increase in height may appear small, it is likely underestimated given that many studies were of short duration and included older adolescents, potentially after epiphyseal growth plate closure. But more prospective large trials are needed to confirm.**

### C-Peptide and Islet Autoantibodies as Markers for Risk of Hypoglycemia

Diabetic Medicine: September 2015 Volume 109, Issue 3, Pages 485–492

In patients with Type 2 diabetes, intensive glycaemic control is associated with hypoglycaemia and possibly increased mortality. However, no blood biomarkers exist to predict these outcomes. Using participants from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, we hypothesized that insulin deficiency and islet autoantibodies in patients with clinically diagnosed Type 2 diabetes would be associated with severe hypoglycaemia and death.

A nested case-control study design was used. A case (n = 86) was a participant who died with at least one episode of severe hypoglycaemia, defined as hypoglycaemia requiring assistance, at any point during ACCORD follow-up. A control (n = 344) was a participant who did not die and did not have severe hypoglycaemia during follow-up. Each case was matched to four controls (glycaemic intervention arm, race, age and BMI). Baseline insulin deficiency (fasting C-peptide  $\leq 0.15$  nmol/l) and islet autoantibodies [glutamic acid decarboxylase (GAD), tyrosine phosphatase-related islet antigen 2 (IA2), insulin (IAA) and zinc transporter (ZnT8)] were measured. Conditional logistic regression with and without adjustment for age, BMI and diabetes duration was used.

Death during ACCORD in those who experienced at least one episode of severe hypoglycaemia was associated with insulin deficiency [OR 4.8 (2.1, 11.1):  $P < 0.0001$ ], GAD antibodies [OR 2.3 (1.1, 5.1):  $P = 0.04$ ], the presence of IAA or baseline insulin use [OR 6.1 (3.5, 10.7):  $P < 0.0001$ ], which remained significant after adjusting for age, BMI, and diabetes duration. There was no significant association with IA2 or ZnT8 antibodies.

In patients with Type 2 diabetes, C-peptide or GAD antibodies may serve as blood biomarkers predicting higher odds of subsequent severe hypoglycaemia and death

#### Editor's comment

**In Type 2 diabetes, intensive glycaemic control may lead to hypoglycaemia and increased mortality. However, no blood biomarkers to predict these outcomes has not been specified. Blood samples from patients who had died and had at least one reported episode of severe hypoglycemia during the course of the ACCORD study were compared with blood samples from living participants who had not experienced severe hypoglycemia. Death and hypoglycemia were seen to be associated with islet autoantibodies (glutamic acid decarboxylase autoantibodies; OR, 2.3) and insulin deficiency (OR, 4.8).**

## Pioglitazone treatment and cardiovascular event and death in subjects with type 2 diabetes without established cardiovascular disease

H Yokoyama, S Araki, K Kawai, K Hirao, M Oishi, K Sugimoto, H Sone, H Maegawa, A Kashiwagi, on behalf of Japan Diabetes Clinical Data Management Study Group (JDDM 36), Published Online: July 15, 2015 DOI: <http://dx.doi.org/10.1016/j.diabres.2015.06.005>

The protective association of pioglitazone with cardiovascular events and death was investigated over 6-years in large-scale type 2 diabetic subjects without established cardiovascular disease in a primary care setting.

A six-year observational cohort study including 2864 subjects with type 2 diabetes without established cardiovascular disease was performed. The primary endpoint was a composite of first occurrence of cardiovascular disease or death. The effect of pioglitazone use at a baseline year with a Cox proportional hazard model and the time-dependent use in each one-year examination interval with a pooled logistic regression model were analyzed.

Baseline use of pioglitazone (n = 493) did not show a statistically protective effect on the primary endpoint (n = 175), although it tended to reduce the risk (adjusted hazard ratio 0.67 [95% CI: 0.43–1.05]). However, pooled logistic regression analysis indicated a significant protective association of pioglitazone with the primary endpoint (0.58 [0.38 to 0.87]) and cardiovascular disease (0.54 [0.33–0.88]), independent of concurrent levels of blood glucose, blood pressure, lipids, albuminuria, and renal function. In particular, this protective association was observed in those with diabetic nephropathy regardless of the daily dose of pioglitazone. Among a total of 898 subjects who took pioglitazone during the period, 43% experienced a discontinuation at least once; however, serious adverse effects were rare.

### Editor's comment

**This observational study indicated a protective association of pioglitazone with cardiovascular disease and death in type 2 diabetic subjects without established vascular disease, particularly those with nephropathy. There are many evidences in support of cardio-protective action of Pioglitazone. This study views strongly the existing knowledge of cardio protection of Pioglitazone in presence of nephropathy even.**

## Taking Blood Pressure Drugs at Night May Help Prevent Type 2 Diabetes

Ramon Hermida, Zachary Bloomgarden, Sept. 23, 2015, Diabetologia, online

The timing of taking your blood pressure medicine could have a big impact on whether or not one will develop type 2 diabetes. These Spanish researchers found that taking blood pressure medications at bedtime rather than taking at morning may cut the risk of developing type 2 diabetes by more than half.

People with high blood pressure tend to suffer from a phenomenon called “non-dipping,” in which their blood pressure does not substantially decrease during sleep as it does in healthy people. The investigators found that “non-dippers” tended to have an increased risk of developing type 2 diabetes, compared with people whose blood pressure decreased normally during sleep.

A follow-up clinical trial by the same research group revealed that taking high blood pressure medications right before bed helped lower a person's sleeping blood pressure, and the risk of type 2 diabetes. For every 14-point decrease in a person's average sleeping systolic blood pressure, they experienced a 30 percent reduction in their risk of developing type 2 diabetes.

The results indicate lowering asleep blood pressure could indeed be a significant method for reducing the risk of developing type 2 diabetes.

Questions may be raised how are these two very different diseases connected? Hormones such as adrenaline and angiotensin play a role in the development of both high blood pressure and type 2 diabetes. A number of blood pressure medications specifically target angiotensin, a hormone that causes blood vessels to constrict and blood pressure to rise. Angiotensin also contributes to increased glucose (sugar) release from the liver and decreased insulin sensitivity. These factors can lead to type 2 diabetes.

Drugs that target angiotensin include angiotensin receptor blockers (ARBs), ACE inhibitors and beta blockers. All three classes of medications were associated with a reduced risk of type 2 diabetes when taken at bedtime.

After showing that reduced blood pressure during sleep was associated with lower risk of type 2 diabetes, the researchers decided to see whether taking an entire daily dose of one or more blood pressure medications at bedtime could drive a person's type 2 diabetes risk down even more.

The clinical trial involved more than 2,000 people who had high blood pressure but not diabetes. They were randomly assigned to take all their blood pressure medications either first thing in the morning or right before bed. During an average six-year follow up, 171 of the participants developed type 2 diabetes.

In the study volunteers in the bedtime-treatment group there was a significant reduction in their sleeping blood pressure, with "non-dipping" occurring in only 32 percent of their group, compared with 52 percent of the patients who took their medication in the morning, according to the study results.

The study found the risk of developing type 2 diabetes was 57 percent lower in the bedtime-treated group than the morning group after adjusting for other complicating factors.

Specifically, the odds of type 2 diabetes dropped 61 percent for people taking angiotensin receptor blockers at bedtime compared to morning. For those on ACE inhibitors at night, the odds went down 69 percent. People on beta blockers reduced their odds of the blood sugar disease by 65 percent when they took their medicine at night, the researchers reported.

#### **Editor's Comment**

**Intake of antihypertensive medications at bedtime, instead of upon awakening in the morning, improved asleep blood pressure control and markedly reduced the risk of type 2 diabetes.**

**Earlier studies have failed to show any type 2 diabetes prevention benefit from blood pressure medications, but they may have been flawed because people were asked to take the drugs in the morning. Usually medicines are taken in the morning and not at night. But maybe the ideal time for blood pressure treatment is night.**

#### **Effect of Pioglitazone Medication on the Incidence of Dementia**

MT Heneka, A Fink, G Doblhammer Ann. Neurol 2015 Aug 01;78(2)284-86.

A study was performed on 145,928 people aged  $\geq 60$  years who were free of dementia and insulin-dependent diabetes mellitus at baseline. Over 6 years of follow-up, long-term use of pioglitazone was associated with a lower incidence of dementia (RR, 0.53). Use of pioglitazone for  $< 2$  years did not have a significant effect on the incidence of dementia.

Using observational data from 2004-2010, the study group analyzed the association of pioglitazone and incidence of dementia in a prospective cohort study of 145,928 subjects aged  $\geq 60$  years who, at baseline, were free of dementia and insulin-dependent diabetes mellitus. They distinguished between nondiabetics, diabetics without

pioglitazone, diabetics with prescriptions of <8 calendar quarters of pioglitazone, and diabetics with  $\geq 8$  quarters. Cox proportional hazard models explored the relative risk (RR) of dementia incidence dependent on pioglitazone use adjusted for sex, age, use of rosiglitazone or metformin, and cardiovascular comorbidities.

Long-term use of pioglitazone was associated with a lower dementia incidence. Relative to nondiabetics, the cumulative long-term use of pioglitazone reduced the dementia risk by 47% (RR=0.53,  $p=0.029$ ). If diabetes patients used pioglitazone <8 quarters, the dementia risk was comparable to those of nondiabetics (RR=1.16,  $p=0.317$ ), and diabetes patients without a pioglitazone treatment had a 23% increase in dementia risk (RR=1.23,  $p<0.001$ ). There was no evidence for age effects, nor for selection into pioglitazone treatment due to obesity.

#### Editorial comment

**PPAR receptor  $\gamma$ -activating drugs show various salutary effects in preclinical models of neurodegenerative disease. This trial has shown the protecting role of Pioglitazone in prevention of dementia, of course when continued beyond 2 years. These findings indicate that pioglitazone treatment is associated with a reduced dementia risk in initially non-insulin-dependent diabetes mellitus patients. Prospective clinical trials are needed to evaluate a possible neuroprotective effect in these patients in an ageing population.**

### Troponin and Cardiac Events in Stable Ischemic Heart Disease and Diabetes

N. Engl. J. Med 2015 Aug 13;373(7):610-20, BM Everett, MM Brooks, HE Vlachos, BR Chaitman, RL Frye, DL Bhatt

Cardiac troponin concentrations are used to identify patients who would benefit from urgent revascularization for acute coronary syndromes. The study group hypothesized that they might be used in patients with stable ischemic heart disease to identify those at high risk for cardiovascular events who might also benefit from prompt coronary revascularization.

They measured the cardiac troponin T concentration at baseline with a high-sensitivity assay in 2285 patients who had both type 2 diabetes and stable ischemic heart disease and were enrolled in the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes trial. They tested for an association between the troponin T concentration and a composite end point of death from cardiovascular causes, myocardial infarction, or stroke. They then evaluated whether random assignment to prompt revascularization reduced the rate of the composite end point in patients with an abnormal troponin T concentration ( $\geq 14$  ng per liter) as compared with those with a normal troponin T concentration ( $<14$  ng per liter).

Of the 2285 patients, 2277 (99.6%) had detectable ( $\geq 3$  ng per liter) troponin T concentrations and 897 (39.3%) had abnormal troponin T concentrations at baseline. The 5-year rate of the composite end point was 27.1% among the patients who had had abnormal troponin T concentrations at baseline, as compared with 12.9% among those who had had normal baseline troponin T concentrations. In models that were adjusted for cardiovascular risk factors, severity of diabetes, electrocardiographic abnormalities, and coronary anatomy, the hazard ratio for the composite end point among patients with abnormal troponin T concentrations was 1.85 (95% confidence interval [CI], 1.48 to 2.32;  $P<0.001$ ). Among patients with abnormal troponin T concentrations, random assignment to prompt revascularization, as compared with medical therapy alone, did not result in a significant reduction in the rate of the composite end point (hazard ratio, 0.96; 95% CI, 0.74 to 1.25).

The cardiac troponin T concentration was an independent predictor of death from cardiovascular causes, myocardial infarction, or stroke in patients who had both type 2 diabetes and stable ischemic heart disease. An abnormal troponin T value of 14 ng per liter or higher did not identify a subgroup of patients who benefited from random assignment to prompt coronary revascularization.

**Editor's comment**

This study examined whether increased cardiac troponin T concentrations can identify patients with both type 2 diabetes and stable ischemic heart disease who are at high risk for cardiovascular events, and who might benefit from coronary revascularization. The 5 year composite endpoint consisted of death from cardiovascular causes, myocardial infarction, or stroke and was higher among patients with baseline troponin levels of  $\geq 14$  ng/L (27.1%) in comparison with those who had a normal troponin level of  $< 14$  ng/L (12.9%) at baseline. A troponin concentration of  $\geq 14$  ng/L in patients assigned to prompt revascularization was not associated in a reduction in the rate of the composite endpoint. Cardiac troponin T concentrations of  $\geq 14$  ng/L independently predicted death from cardiovascular causes, myocardial infarction, or stroke in patients with type 2 diabetes and stable ischemic heart disease. However, an abnormally high troponin concentration was not an indicator of whether patients would benefit from coronary revascularization.

### Cardiovascular and Heart Failure Safety Profile of Vildagliptin: A Meta-Analysis of 17,000 Patients

Diabetes Obes Metab 2015 Aug 07;[Epub Ahead of Print], G McInnes, M Evans, S Del Prato, M Stumvoll, A Schweizer, V Lukashevich, Q Shao, W Kothny

A retrospective meta-analysis of prospectively adjudicated CV events. Patient-level data were pooled from 40 double-blind, randomised-controlled phase III and IV vildagliptin studies. The primary endpoint was occurrence of major adverse CV events (MACE; myocardial infarction, stroke and CV death). Assessments of the individual MACE components and HF events (requiring hospitalisation or new onset) were secondary endpoints. The risk ratio (RR) of vildagliptin (50 mg once- and twice-daily combined) versus comparators (placebo and all non-vildagliptin treatments) was calculated using a Mantel-Haenszel (M-H) method.

Of the 17,446 patients, 9599 received vildagliptin (9251.4 subject-year exposure [SYE]) and 7847 received comparators (7317.0 SYE). The mean age was 57 years, body mass index 30.5 kg/m<sup>2</sup> (nearly 50% obese), HbA1c 8.1% and T2DM duration 5.5 years. A MACE occurred in 83 (0.86%) vildagliptin-treated patients and 85 (1.20%) comparator-treated patients, with M-H RR of 0.82 (95% CI, 0.61 to 1.11). Similar RRs were observed for the individual events. Confirmed HF events were reported in 41 (0.43%) vildagliptin-treated patients and 32 (0.45%) comparator-treated patients, M-H RR 1.08 (95% CI, 0.68 to 1.70).

This large meta-analysis indicates that vildagliptin is not associated with an increased risk for adjudicated MACE relative to comparators.

**Editor's comment**

There is a continuing debate surrounding the cardiovascular (CV) and particularly heart failure safety profile of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes mellitus (T2DM). A large meta-analysis was performed on the records of 17,446 diabetic individuals. Those who received vildagliptin (n = 9599) had a risk ratio for major adverse cardiovascular events of 0.82 (95% CI, 0.61–1.11). Vildagliptin was not associated with an increased risk for major adverse cardiovascular events or heart failure. This analysis also did not find a significant increased risk of Heart Failure in vildagliptin-treated patients.

### Comparison of basal insulin therapies regarding the risk of acute myocardial infarction in type 2 diabetic patients: an observational cohort study

Bianca Kollhorst, Sigrid Beh, Dirk Enders, Franz-Werner Dippel, Karlheinz Theobald and Edeltraut Garbe\*

Diabetes, Obesity and Metabolism .DOI: 10.1111/dom.12554

The study aimed to assess the risk of acute myocardial infarction (AMI) in patients with type 2 diabetes mellitus treated with long-acting insulin analogs in comparison to other basal insulin therapy. They used German insurance claims data from the years 2004–2009 to conduct a study in a retrospective cohort of type 2 diabetic patients. Naïve insulin users were defined as patients who had an insulin-free history before the first prescription of long-acting analog insulin, human neutral protamine Hagedorn (NPH) insulin or premixed insulin and who were pretreated with oral antidiabetic drugs. Adjusted hazard ratios (HRs) of AMI and corresponding 95%-confidence intervals (CI) were calculated by sex-stratified Cox models. Propensity-score-matched analyses were conducted as sensitivity analyses.

They identified 21,501 new insulin users. Patients treated with premixed insulin were older than patients treated with analog or NPH insulin (mean age 70.7 vs. 64.1 and 61.6 years) and had more comorbidities. Regarding the risk of AMI, adjusted HRs revealed no statistically significant difference between NPH and analog insulin (HR: 0.94, 95%-CI: 0.74-1.19), but a higher risk for premixed compared to analog insulin (HR: 1.27, 95%-CI: 1.02-1.58). Contrary to the primary analysis, the propensity-score-matched analysis did not show an increased risk for premixed insulin.

**Editor's comment**

**No difference was observed for the risk of AMI between long-acting analog and NPH insulin in this study. Neither long-acting analog insulin nor premix insulin appears to be associated with AMI in patients with type 2 diabetes.**

**Relation of Smoking With Total Mortality and Cardiovascular Events Among Patients With Diabetes: A Meta-Analysis and Systematic Review**

Circulation 2015 Aug 26;[Epub Ahead of Print], A Pan, Y Wang, M Talaei, FB H

Prevalence of smoking in diabetic patients remains high, and reliable quantification of the excess mortality and morbidity risks associated with smoking is important for diabetes management. We performed a systematic review and meta-analysis of prospective cohort studies to evaluate the relation of active smoking with risk of total mortality and cardiovascular events among diabetic patients.

A total of 89 cohort studies were included. The pooled adjusted RR (95% confidence interval [CI]) associated with smoking was 1.55 (1.46-1.64) for total mortality (48 studies with 1,132,700 participants and 109,966 deaths), and 1.49 (1.29-1.71) for cardiovascular mortality (13 studies with 37,550 participants and 3,163 deaths). The pooled RR (95% CI) was 1.44 (1.34-1.54) for total cardiovascular disease (CVD; 16 studies), 1.51 (1.41-1.62) for coronary heart disease (CHD; 21 studies), 1.54 (1.41-1.69) for stroke (15 studies), 2.15 (1.62-2.85) for peripheral arterial disease (3 studies), and 1.43 (1.19-1.72) for heart failure (4 studies). Compared to never smokers, former smokers were at a moderately elevated risk of total mortality (1.19; 1.11-1.28), cardiovascular mortality (1.15; 1.00-1.32), CVD (1.09; 1.05-1.13) and CHD (1.14; 1.00-1.30), but not for stroke (1.04; 0.87-1.23).

**Editor's comment**

**In this meta-analysis, evaluation of patients with diabetes was done to determine the association of active smoking with mortality and cardiovascular events. They found that smoking was associated with a relative risk of 1.55 for mortality, 1.49 for cardiovascular mortality, and 1.44 for total cardiovascular disease. Former smokers had a relative risk of 1.19 for total mortality and 1.09 for cardiovascular disease when compared with never smokers. Active smoking is associated with significantly increased risks of total mortality and cardiovascular events among diabetic patients, while smoking cessation was associated with reduced risks compared to current smoking. The findings provide strong evidence for the recommendation of quitting smoking among diabetic patients.**

### **Use of Antibiotics and Risk of Type 2 Diabetes: A Population-Based Case-Control Study**

J. Clin. Endocrinol. Metab. 2015 Aug 27;[Epub Ahead of Print], KH Mikkelsen, FK Knop, M Frost, J Hallas, A Pottegård

Evidence that bacteria in the human gut may influence nutrient metabolism is accumulating. We investigated whether use of antibiotics influences the risk of developing type 2 diabetes and whether the effect can be attributed to specific types of antibiotics.

They conducted a population-based case-control study of incident type 2 diabetes cases in Denmark (population 5.6 million) between January 1, 2000, and December 31, 2012. Data from the Danish National Registry of Patients, the Danish National Prescription Registry, and the Danish Person Registry were combined.

The odds ratio (OR) associating type 2 diabetes with exposure to antibiotics of any type was 1.53 (95% confidence interval 1.50-1.55) with redemption of more than or equal to 5 versus 0-1 prescriptions. Although no individual group of antibiotics was specifically associated with type 2 diabetes risk, slightly higher ORs for type 2 diabetes were seen with narrow-spectrum and bactericidal antibiotics (OR 1.55 and 1.48) compared to broad-spectrum and bacteriostatic types of antibiotics (OR 1.31 and 1.39), respectively. A clear dose-response effect was seen with increasing cumulative load of antibiotics. The increased use of antibiotics in patients with type 2 diabetes was found up to 15 years before diagnosis of type 2 diabetes as well as after the diagnosis.

**Editor's comment**

**In incident type 2 diabetes, the authors investigated whether antibiotic use influences the risk of developing diabetes and whether any effect can be attributed to specific types of antibiotics. An odds ratio of 1.53 was found for type 2 diabetes and exposure to any type of antibiotics. No group of antibiotics was specifically associated with risk of type 2 diabetes, but slightly higher odds ratios were seen with narrow-spectrum and bactericidal antibiotics compared with broad-spectrum and bacteriostatic antibiotics.**

**A dose-response effect was seen with increasing cumulative antibiotic load. The results of this study indicate that antibiotic exposure increases risk of type 2 diabetes; however, the authors caution that the findings may also be due to an increased demand for antibiotics from patients with as-yet-undiagnosed diabetes due to their increased risk of infection.**

### **Gestational Diabetes Mellitus Can Be Prevented by Lifestyle Intervention: The Finnish Gestational Diabetes Prevention Study (RADIEL): A Randomized Controlled Trial;**

Koivusalo S, Rönö K, Klemetti M, Roine R, Lindström J, Erkkola M, Kaaja R, Pöyhönen-Alho M, Tiitinen A, Huvinen E, Andersson S, Laivuori H, Valkama A, Meinilä J, Kautiainen H, Eriksson J, Stach-Lempinen B; Diabetes Care (Jul 2015)



Two hundred ninety-three women with a history of GDM and/or a pre-pregnancy BMI of  $\geq 30$  kg/m<sup>2</sup> were enrolled in the study at <20 weeks of gestation and were randomly allocated to the intervention group (n = 155) or the control group (n = 138). Each subject in the intervention group received individualized counselling on diet, physical activity, and weight control from trained study nurses, and had one group meeting with dietitian. The control group received standard antenatal care. The diagnosis of GDM was based upon a 75-g, 2-h oral glucose tolerance test at 24-28 weeks of gestation.

A total of 269 women were included in the analyses. The incidence of GDM was 13.9% in the intervention group and 21.6% in the control group ([95% CI 0.40-0.98%] P = 0.044, after adjustment for age, pre-pregnancy BMI, previous GDM status, and the number of weeks of gestation). Gestational weight gain was lower in the intervention group (-0.58 kg [95% CI -1.12 to -0.04 kg] adjusted P = 0.037). Women in the intervention group increased their leisure time physical activity more and improved their dietary quality, compared with the women in the control group.

**Editor's comment**

**This study assessed whether gestational diabetes mellitus (GDM) can be prevented by a moderate lifestyle intervention in pregnant women who are at high risk for the disease. A moderate individualized lifestyle intervention reduced the incidence of GDM by 39% in high-risk pregnant women. These findings are stimulatory and may have major health consequences for both the mother and the child.**

**Potential Mechanisms of Ketoacidosis Associated With Use of SGLT2 Inhibitors**

**J. Clin. Endocrinol. Metab.; 2015 Jun 18; Epub Ahead of Print; SI Taylor, JE Blau, KI Rothe**

SGLT2 inhibitors are antidiabetic drugs that increase urinary excretion of glucose, thereby improving glycemic control and promoting weight loss. Since approval of the first-in-class drug in 2013, data have emerged suggesting that these drugs increase the risk of diabetic ketoacidosis. In May, 2015, the FDA issued a warning that SGLT2 inhibitors may lead to ketoacidosis.

SGLT2 inhibitors trigger multiple mechanisms that could predispose to diabetic ketoacidosis. When SGLT2 inhibitors are combined with insulin, it is often necessary to decrease the insulin dose to avoid hypoglycemia. The lower dose of insulin may be insufficient to suppress lipolysis and ketogenesis. Furthermore, SGLT2 is expressed in pancreatic alpha cells, and SGLT2 inhibitors promote glucagon secretion. Finally, phlorizin, a non-selective inhibitor of SGLT-family transporters decreases urinary excretion of ketone bodies. A decrease in renal clearance of ketone bodies could also increase plasma ketone body levels.

**Editor's comment**

**SGLT2 inhibitors have been associated with an increased risk of ketoacidosis. The exact mechanism for this effect is unclear. The reduced dose of insulin used by patients receiving SGLT2 inhibitors may be insufficient to suppress ketogenesis. SGLT2 inhibitors can promote glucagon secretion and decrease urinary excretion of ketone bodies. A combination of these and other mechanisms may be responsible for the increased risk of ketoacidosis.**

**Further research is needed to clarify the factors that contribute to ketoacidosis and treatment strategies to minimize the risk.**

**Intake of Saturated and Trans-Unsaturated Fatty Acids and Risk of All Cause Mortality, Cardiovascular Disease, and Type 2 Diabetes: Systematic Review and Meta-Analysis of Observational Studies**

BMJ 2015 Aug 12;351(xx)h3978, RJ de Souza, A Mente, A Maroleanu, AI Cozma, V Ha, T Kishibe, E Uleryk, P Budykowski, H Schünemann, J Beyene, SS Anand

The meta analysis was aimed to systematically review associations between intake of saturated fat and trans unsaturated fat and all cause mortality, cardiovascular disease (CVD) and associated mortality, coronary heart disease (CHD) and associated mortality, ischemic stroke, and type 2 diabetes.

Observational studies reporting associations of saturated fat and/or trans unsaturated fat (total, industrially manufactured, or from ruminant animals) with all cause mortality, CHD/CVD mortality, total CHD, ischemic stroke, or type 2 diabetes.

For saturated fat, three to 12 prospective cohort studies for each association were pooled (five to 17 comparisons with 90 501-339 090 participants). Saturated fat intake was not associated with all cause mortality (relative risk 0.99, 95% confidence interval 0.91 to 1.09), CVD mortality (0.97, 0.84 to 1.12), total CHD (1.06, 0.95 to 1.17), ischemic stroke (1.02, 0.90 to 1.15), or type 2 diabetes (0.95, 0.88 to 1.03). There was no convincing lack of association between saturated fat and CHD mortality (1.15, 0.97 to 1.36;  $P=0.10$ ). For trans fats, one to six prospective cohort studies for each association were pooled (two to seven comparisons with 12 942-230 135 participants). Total trans fat intake was associated with all cause mortality (1.34, 1.16 to 1.56), CHD mortality (1.28, 1.09 to 1.50), and total CHD (1.21, 1.10 to 1.33) but not ischemic stroke (1.07, 0.88 to 1.28) or type 2 diabetes (1.10, 0.95 to 1.27). Industrial, but not ruminant, trans fats were associated with CHD mortality (1.18 (1.04 to 1.33) v 1.01 (0.71 to 1.43)) and CHD (1.42 (1.05 to 1.92) v 0.93 (0.73 to 1.18)). Ruminant trans-palmitoleic acid was inversely associated with type 2 diabetes (0.58, 0.46 to 0.74). The certainty of associations between saturated fat and all outcomes was “very low.” The certainty of associations of trans fat with CHD outcomes was “moderate” and “very low” to “low” for other associations.

Saturated fats are not associated with all cause mortality, CVD, CHD, ischemic stroke, or type 2 diabetes, but the evidence is heterogeneous with methodological limitations. Trans fats are associated with all cause mortality, total CHD, and CHD mortality, probably because of higher levels of intake of industrial trans fats than ruminant trans fats. Dietary guidelines must carefully consider the health effects of recommendations for alternative macronutrients to replace trans fats and saturated fats.

#### Editor's comment

**In a meta-analysis of nutrition studies, intake of saturated fat was not associated with all-cause mortality, mortality due to cardiovascular disease, or type 2 diabetes. Total trans-fat intake was associated with all-cause mortality and mortality due to coronary heart disease, but was not associated with type 2 diabetes.**

**Further research is necessary to better refine dietary guidelines.**

### **Long-term changes in sleep duration, energy balance and risk of type 2 diabetes. Diabetologia pp 1-9, First online: 02 November 2015. Elizabeth M. Cespedes , Shilpa N. Bhupathiraju, Yanping Li, Bernard Rosner, Susan Redline, Frank B. Hu**

The cohort includes 59,031 women aged 55–83 years in the Nurses' Health Study without diabetes in 2000. Change in sleep duration is the difference between self-reported 24 h sleep duration in 1986 and 2000. Diet, physical activity and covariates were updated every 2–4 years. Self-reported diabetes was confirmed via validated questionnaires. Cox regression models were adjusted for 1986 sleep duration and 1986 values of diabetes risk factors, including BMI, and subsequently for change in covariates from 1986 to 2000.

They documented 3,513 incident diabetes cases through to 2012. Compared with no change, decreases in sleep duration were adversely associated with changes in diet quality and physical activity, while increases were associated with greater weight gain. After adjustment for 1986 covariates, HRs (95% CI) for  $\leq -2$ ,  $> -2$  to  $< 0$ ,  $> 0$  to  $< 2$  and  $\geq 2$  h/day changes in sleep duration (vs no change) were 1.09 (0.93, 1.28), 1.10 (1.001, 1.12), 1.09 (1.00, 1.18) and 1.30 (1.14, 1.46), respectively. Additional adjustment for diet and physical activity did not appreciably alter the results. Increases in sleep duration  $\geq 2$  h/day remained adversely associated with diabetes (HR [95% CI]: 1.15 [1.01, 1.30]) after adjustment for change in covariates, including BMI.

**Editor's comment**

**Baseline sleep duration has a U-shaped relationship with type 2 diabetes, but little research examines the associated changes. This study examined long-term changes in sleep duration and concomitant changes in diet, physical activity, weight and subsequent diabetes. Increases in sleep duration among middle-aged and older women were modestly associated with risk of diabetes; changes in diet, physical activity and BMI did not explain associations.**

**Continuation or Discontinuation of Pioglitazone When Starting Bedtime Insulin in Patients With Poorly Controlled Type 2 Diabetes in an Inner-City Population**

J. Diabetes Complicat. 2015 Jun 30;[Epub Ahead of Print], M Mojtahedzadeh, ML Lee, TC Friedman

The study group assessed the impact of continuing versus discontinuing pioglitazone on hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), and weight when starting bedtime insulin in patients with poor glycemic control.

They retrospectively analyzed data from a 13-month randomized control trial on 77 patients with type 2 diabetes mellitus (DM), who despite maximum doses of three oral diabetes medications (metformin, sulfonylurea and pioglitazone) had HbA1C levels above 7.5%. Patients were randomized to either continuing or discontinuing pioglitazone in addition to starting and up-titrating bedtime insulin. HbA1C, FPG, and weight were assessed at baseline, 3months, 7months and 13months with the differences from baseline for the two groups compared at each of the three time points using the Wilcoxon rank sum test.

They found that HbA1c was significantly lower at the 7-month ( $p=0.01$ ) and 13-month time points ( $p=0.036$ ), and FPG was significantly lower at all three time points in the group continuing pioglitazone compared with those discontinuing pioglitazone. Continuing pioglitazone resulted in a greater increase in weight at the 3-month ( $p=0.002$ ), 7-month ( $p=0.0001$ ) and 13-month ( $p=0.00003$ ) time points. Patients with the lowest HbA1c ( $<8.2\%$ ) at baseline were more likely to benefit from continuing pioglitazone than those with higher baseline HbA1c. Patients who started insulin and discontinued pioglitazone had similar HbA1c, FPG and weight at the three time points as at baseline, suggesting that pioglitazone and bedtime insulin has similar glycemic effect in this population.

The conclusion of this study is that in patients with uncontrolled type 2 DM, continuing pioglitazone while concurrently starting bedtime insulin within a 13-month period led to a significant decrease in both HbA1c and FPG levels compared with those who did not receive pioglitazone; however weight increased during this period.

**Editor's comment**

**Insulin treatment at bedtime was prescribed for a group of patients whose diabetes was inadequately controlled (HbA1c  $>7.5\%$ ) despite treatment with metformin, sulfonylurea, and pioglitazone. Patients were randomized to either continue or discontinue pioglitazone during therapy with metformin, sulfonylurea, and bedtime insulin. Patients who continued pioglitazone therapy had lower levels of HbA1c and fasting blood glucose and greater weight gain than patients who discontinued pioglitazone. Among type 2 diabetics with inadequate glycemic control, maintaining pioglitazone therapy when adding insulin therapy improved glycemic control.**

**Lifetime Risk of Developing Impaired Glucose Metabolism and Eventual Progression From Prediabetes to Type 2 Diabetes: A Prospective Cohort Study**

Lancet Diabetes Endocrinol 2015 Nov 10;[Epub Ahead of Print], S Ligthart, TT van Herpt, MJ Leening, M Kavousi, A Hofman, BH Stricker, M van Hoek, EJ Sijbrands, OH Franco, A Dehghan.

This study of prospective population-based cohort analysis aimed to calculate the lifetime risk of the full range of glucose impairments, from normoglycaemia to prediabetes, type 2 diabetes, and eventual insulin use. They used data from the population-based Rotterdam Study and identified diagnostic events by use of general practitioners' records, hospital discharge letters, pharmacy dispensing data, and serum fasting glucose measurements taken at the study centre (Rotterdam, Netherlands) visits. Normoglycaemia, prediabetes, and diabetes were defined on the basis of WHO criteria for fasting glucose (normoglycaemia:  $\leq 6.0$  mmol/L; prediabetes:  $>6.0$  mmol/L and  $<7.0$  mmol/L; and diabetes  $\geq 7.0$  mmol/L or use of glucose-lowering drug). They calculated lifetime risk using a modified version of survival analysis adjusted for the competing risk of death and also estimated the lifetime risk of progression from prediabetes to overt diabetes and from diabetes free of insulin treatment to insulin use. In addition, they calculated years lived with healthy glucose metabolism.

There were 10 050 participants from the Rotterdam Study. During a follow-up of up to 14.7 years (between April 1, 1997, and Jan 1, 2012), 1148 participants developed prediabetes, 828 developed diabetes, and 237 started insulin treatment. At age 45 years, the remaining lifetime risk was 48.7% (95% CI 46.2–51.3) for prediabetes, 31.3% (29.3–33.3) for diabetes, and 9.1% (7.8–10.3) for insulin use. In individuals aged 45 years, the lifetime risk to progress from prediabetes to diabetes was 74.0% (95% CI 67.6–80.5), and 49.1% (38.2–60.0) of the individuals with overt diabetes at this age started insulin treatment. The lifetime risks attenuated with advancing age, but increased with increasing BMI and waist circumference. On average, individuals with severe obesity lived 10 fewer years without glucose impairment compared with normal-weight individuals.

Impaired glucose metabolism is a substantial burden on population health, and these findings emphasise the need for more effective prevention strategies, which should be implemented as soon in a person's life as possible. The substantial lifetime risk of prediabetes and diabetes in lean individuals also supports risk factor control in non-obese individuals.

#### Editor's comment

**Prospective data about fate of prediabetes is minimum. This was a prospective cohort study of 10,050 participants with a follow-up of up to 14.7 years. At age 45 years, the lifetime risks for developing prediabetes, type 2 diabetes, and insulin use were 48.7%, 31.3%, and 9.1%, respectively. An association was noted between increasing BMI or waist circumference and risk of developing glucose impairment. Results show that nearly half of people aged 45 years will go on to develop prediabetes, and nearly one-third will develop diabetes. This study is an eye opener for diabetes prevention in the community.**

### Efficacy and Safety of Once-Weekly Glucagon-Like Peptide 1 Receptor Agonists for the Management of Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Diabetes Obes Metab 2015 Nov 01;17(11)1065-1074, T Karagiannis, A Liakos, E Bekiari, E Athanasiadou, P Paschos, D Vasilakou, M Mainou, M Rika, P Boura, DR Matthews, A Tsapas .

This study assessed the efficacy and safety of recently approved once-weekly glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in patients with type 2 diabetes.

The study group conducted a systematic review and meta-analysis of randomized controlled trials comparing any GLP-1 RA licensed for once-weekly dosing (albiglutide, dulaglutide or exenatide extended release) with placebo or other antidiabetic agents. In this systematic review 33 trials were included with a total of 16 003 participants. Compared with placebo the change in glycated haemoglobin (HbA1c) concentration was -0.66% [six studies; 95% confidence interval (CI) -1.14 to -0.19; I(2) = 88%] with albiglutide, and -1.18% (seven studies; 95% CI -1.34 to -1.02; I(2) = 65%) with dulaglutide. Based on data from placebo-controlled trials, we did not detect statistically significant weight-sparing benefits for albiglutide or dulaglutide.

Compared with other antidiabetic agents, once-weekly GLP-1 RAs outperformed sitagliptin, daily exenatide and insulin glargine in terms of HbA1c-lowering (mean differences -0.40%; 95% CI -0.66 to -0.14; I(2) =85%, -0.44%; 95% CI -0.58 to -0.29; I(2) =40% and -0.28; 95% CI -0.45 to -0.10; I(2) =81%, respectively). The main adverse effects of treatment included gastrointestinal and injection site reactions.

**Editor's comment**

**The efficacy and safety of once-weekly GLP-1 receptor agonists were evaluated in this systematic review and meta-analysis of 33 randomized controlled trials including 16,000 individuals. Weekly dosed GLP-1 receptor agonists decreased HbA1c significantly when compared with placebo or with sitagliptin, insulin glargine, and exenatide (dosed daily) and appear to provide a useful alternative for treatment of type 2 diabetes. Thus it appears that considering their dosing scheme and overall efficacy and safety profile, once-weekly GLP-1 RAs are a convenient therapeutic option for use as add-on to metformin.**

**Durability and Tolerability of Dapagliflozin Over 52 weeks as Add-On to Metformin and Sulphonylurea in Type 2 Diabetes**

Diabetes Obes Metab 2015 Nov 01;17(11)1075-1084, S Matthaai, K Bowering, K Rohwedder, J Sugg, S Parikh, E Johnsson

This study targeted to evaluate the safety and efficacy of dapagliflozin as add-on therapy to metformin plus sulphonylurea over 52 weeks. Patients with type 2 diabetes mellitus (T2DM) using sulphonylurea and metformin received dapagliflozin 10mg/day or placebo added to therapy for 52 weeks (24-week randomized, double-blind period plus 28-week double-blind extension).

A total of 219 patients were randomized 1: 1 to dapagliflozin or placebo. Over 52 weeks, glycated haemoglobin (HbA1c) and fasting plasma glucose levels showed greater improvement from baseline with dapagliflozin (-0.8% and -1.5 mmol/l) than with placebo (-0.1% and 0.6mmol/l). More patients achieved HbA1c <7.0% with dapagliflozin (27.3%) than with placebo (11.3%) at 52 weeks. Dapagliflozin was associated with greater reductions in body weight and systolic blood pressure (-2.9kg and -1.0mmHg) compared with placebo (-1.0kg and 1.1 mmHg). Greater increases in total, LDL and HDL cholesterol and decreases in triglycerides were observed with dapagliflozin (3.4, 4.8, 6.9 and -8.0%, respectively) versus placebo (1.4, 0.9, 0.6 and 2.9%, respectively). Fewer patients were rescued for failing to reach glycaemic targets with dapagliflozin (9.3%) than with placebo (44.4%). Adverse events and serious adverse events were similar between groups (dapagliflozin: 69.7 and 6.4%; placebo: 73.4 and 7.3%). More hypoglycaemic events were observed with dapagliflozin (15.6%) than with placebo (8.3%). Genital infections were reported in more patients in the dapagliflozin (10.1%) than in the placebo group (0.9%) and urinary tract infection frequency was similar in the two groups (10.1 and 11.0%).

**Editor's comment**

**This study of 219 patients with type 2 diabetes evaluated the effect of adding dapagliflozin to a treatment regimen of already using sulphonylurea and metformin. For 52 weeks, patients received either dapagliflozin 10 mg daily or placebo. Dapagliflozin was found to be superior in effectiveness than placebo in controlling blood glucose levels and dropping body weight, systolic blood pressure, and triglyceride levels. There were no marked overall differences in adverse effects associated with dapagliflozin vs placebo. This study shows better glucose control provided by addition of dapagliflozin to an already existing treatment regimen of sulphonylurea and metformin in patients with type 2 diabetes.**

## 10-Year Trajectory of $\beta$ -Cell Function and Insulin Sensitivity in the Development of Type 2 Diabetes: A Community-Based Prospective Cohort Study.

Lancet Diabetes Endocrinol 2015 Nov 11;[Epub Ahead of Print], JH Ohn, SH Kwak, YM Cho, S Lim, HC Jang, KS Park, NH Cho

The relative contributions of  $\beta$ -cell function and insulin sensitivity in the pathogenesis of type 2 diabetes are not clearly understood. Ohn et al investigated the longitudinal change in  $\beta$ -cell function and insulin sensitivity in the development of diabetes and the role of genetic variants in deterioration of glucose tolerance. They followed up 4106 participants with normal glucose tolerance (NGT) from the Korean Genome and Epidemiology Study with oral glucose tolerance tests every 2 years for 10 years. They estimated pancreatic  $\beta$ -cell function with the 60 min insulinogenic index (IGI60) and insulin sensitivity with the composite (Matsuda) insulin sensitivity index (ISI). They investigated the association of 66 known type 2 diabetes genetic variants with risk of prediabetes or diabetes and impaired  $\beta$ -cell function and insulin sensitivity.

During 10 years of follow-up, 1093 (27%) of 4106 participants developed prediabetes and 498 (12%) participants developed diabetes. Compared with participants who remained NGT, those who progressed to diabetes had a lower IGI60 (unadjusted data 5.1  $\mu$ U/mmol [95% CI 0.5-56.1] vs 7.9  $\mu$ U/mmol [0.5-113.8];  $p < 0.0001$ ) and lower ISI (unadjusted data 8.2 [2.6-26.0] vs 10.0 [3.2-31.6];  $p < 0.0001$ ) at baseline. Participants who had NGT at 10 years showed a decrease in ISI (adjusted data 10.1 [9.9-10.3] vs 7.4 [7.3-7.6];  $p < 0.0001$ ) but a compensatory increase in IGI60 (adjusted data 6.9  $\mu$ U/mmol [6.5-7.2] vs 11.7  $\mu$ U/mmol [11.2-12.1];  $p < 0.0001$ ) compared with baseline. By contrast, participants who developed diabetes showed a decrease in ISI (adjusted data 8.4 [8.0-8.7] vs 3.0 [2.8-3.2];  $p < 0.0001$ ) but no significant compensatory increase ( $p = 0.95$ ) in IGI60. A genetic variant near the glucokinase gene (rs4607517) was significantly associated with progression to prediabetes or diabetes (hazard ratio 1.27, 1.16-1.38;  $p = 1.70 \times 10^{-7}$ ).

Decreased  $\beta$ -cell function, which might be determined partly by genetic factors, and impaired  $\beta$ -cell compensation for progressive decline in insulin sensitivity are crucial factors in the deterioration of glucose tolerance.

### Editor's comment

**In this Korean study, 4106 participants without diabetes or prediabetes were assessed to determine the pancreatic beta-cell function and insulin sensitivity. The follow-up period was 10 years. A total of 39% of participants developed either prediabetes or diabetes. A resultant increase in beta-cell function due to decreased insulin sensitivity was observed with normal glucose tolerance at 10 years. This subsequent increase in function of beta cells was not observed in patients who developed diabetes at 10 years. Development of diabetes was linked to genetic changes and/or a decrease in beta-cell function and in insulin sensitivity.**

**This study shows that the development of type 2 diabetes mellitus is linked with reduced beta-cell function and insulin sensitivity. It is also associated with loss of the capacity to subsequently increase beta-cell function in response to reduced insulin sensitivity.**

## Association of Early Exposure of Probiotics and Islet Autoimmunity in the TEDDY Study.

JAMA Pediatr 2015 Nov 09;[Epub Ahead of Print], U Uusitalo, X Liu, J Yang, CA Aronsson, S Hummel, M Butterworth, Å Lernmark, M Rewers, W Hagopian, JX She, O Simell, J Toppari, AG Ziegler, B Akolkar, J Krischer, JM Norris, SM Virtanen

Probiotics are thought to affect immunologic responses to environmental exposures by supporting healthy gut microbiota and could therefore theoretically be used to prevent the development of type 1 diabetes mellitus (T1DM)-associated islet autoimmunity. This study was done to examine the association between supplemental probiotic use during the first

year of life and islet autoimmunity among children at increased genetic risk of T1DM.

In this ongoing prospective cohort study that started September 1, 2004, children from 6 clinical centers, 3 in the United States (Colorado, Georgia/Florida, and Washington) and 3 in Europe (Finland, Germany, and Sweden), were followed up for T1DM-related autoantibodies. Blood samples were collected every 3 months between 3 and 48 months of age and every 6 months thereafter to determine persistent islet autoimmunity. Details of infant feeding, including probiotic supplementation and infant formula use, were monitored from birth using questionnaires and diaries. We applied time-to-event analysis to study the association between probiotic use and islet autoimmunity, stratifying by country and adjusting for family history of type 1 diabetes, HLA-DR-DQ genotypes, sex, birth order, mode of delivery, exclusive breastfeeding, birth year, child's antibiotic use, and diarrheal history, as well as maternal age, probiotic use, and smoking. Altogether 8676 infants with an eligible genotype were enrolled in the follow-up study before the age of 4 months. The final sample consisted of 7473 children with the age range of 4 to 10 years (as of October 31, 2014).

Early probiotic supplementation (at the age of 0-27 days) was associated with a decreased risk of islet autoimmunity when compared with probiotic supplementation after 27 days or no probiotic supplementation (hazard ratio [HR], 0.66; 95% CI, 0.46-0.94). The association was accounted for by children with the DR3/4 genotype (HR, 0.40; 95% CI, 0.21-0.74) and was absent among other genotypes (HR, 0.97; 95% CI, 0.62-1.54). Early probiotic supplementation may reduce the risk of islet autoimmunity in children at the highest genetic risk of T1DM. The result needs to be confirmed in further studies before any recommendation of probiotics use is made.

#### Editor's comment

**The authors of this study evaluated the effectiveness of supplemental probiotics during infancy for the prevention of islet autoimmunity in children with genetic risk for type 1 diabetes (T1DM). They found that infants below 27 days of age when were given probiotic supplementation had decreased risk of islet autoimmunity compared with infants who received no probiotics or infants above 27 days of age who received probiotics. They also found that children with the DR3/4 genotype, and not other genotypes, accounted for these results. Children at high risk for T1DM appear to have a reduced risk of developing islet autoimmunity when they are given probiotics in the first month of life.**

### **Consequences of Comorbidity of Elevated Stress and/or Depressive Symptoms and Incident Cardiovascular Outcomes in Diabetes: Results From the REasons for the Geographic And Racial Differences in Stroke (REGARDS) Study**

Diabetes Care 2015 Nov 17;[Epub Ahead of Print], DM Cummings, K Kirian, G Howard, V Howard, Y Yuan, P Muntner, B Kissela, N Redmond, SE Judd, MM Safford

The study evaluated the impact of comorbid depressive symptoms and/or stress on adverse cardiovascular (CV) outcomes in individuals with diabetes compared with those without diabetes. The group examined the relationship between baseline depressive symptoms and/or stress in adults with and without diabetes and physician-adjudicated incident CV outcomes including stroke, myocardial infarction/acute coronary heart disease, and CV death over a median follow-up of 5.95 years in the national REGARDS cohort study.

Subjects included 22,003 adults (4,090 with diabetes) (mean age 64 years, 58% female, 42% black, and 56% living in the southeastern "Stroke Belt"). Elevated stress and/or depressive symptoms were more common in subjects with diabetes (36.8% vs. 29.5%;  $P < 0.001$ ). In fully adjusted models, reporting either elevated stress or depressive symptoms was associated with a significantly increased incidence of stroke (HR 1.57 [95% CI 1.05, 2.33] vs. 1.01 [0.79, 1.30]) and CV death (1.53 [1.08, 2.17] vs. 1.12 [0.90, 1.38]) in subjects with diabetes but not in those without diabetes. The combination of both elevated stress and depressive symptoms in subjects with diabetes was associated with a higher incidence of CV death (2.15 [1.33, 3.47]) than either behavioral comorbidity alone (1.53 [1.08, 2.17]) and higher than in those with both elevated stress and depressive symptoms but without diabetes (1.27 [0.86, 1.88]).

Comorbid stress and/or depressive symptoms are common in individuals with diabetes and together are associated with progressively increased risks for adverse CV outcomes.

#### Editor's comment

This study was designed on 22,003 participants. Amongst them, associations between presence of diabetes, high stress level, and/or symptoms of depression, and likelihood of having poor cardiovascular (CV) results were examined. Diabetics had a significantly increased prevalence of high stress levels and symptoms of depression. Compared with nondiabetics, diabetics with either increased stress or symptoms of depression had an increase in number of new cases of poor CV outcomes. Likewise, diabetics with both increased stress and depression symptoms had an increase in poor CV outcomes when compared with diabetics having either high stress or depressive symptoms. Diabetics with both comorbidities of elevated stress levels and symptoms of depression have an increased likelihood of poor CV outcomes when compared with nondiabetics or with diabetics with either comorbidity alone.

## Changes in Insulin Sensitivity and Insulin Secretion with the Sodium Glucose

### Cotransporter 2 Inhibitor Dapagliflozin

Sunder Mudaliar et al. Diabetes Technology & Therapeutics Volume 16, Number 3, 2014

This randomized, double-blind, placebo-controlled parallel-group study assessed the effects of sodium glucose cotransporter 2 inhibition by dapagliflozin on insulin sensitivity and secretion in subjects with type 2 diabetes mellitus (T2DM), who had inadequate glycemic control with metformin (with or without an insulin secretagogue).

**Subjects and Methods:** Forty-four subjects were randomized to receive dapagliflozin 5mg or matching placebo once daily for 12 weeks. Subjects continued stable doses of background antidiabetes medication throughout the study. Insulin sensitivity was assessed by measuring the glucose disappearance rate (GDR) during the last 40 min of a 5-h hyperinsulinemic, euglycemic clamp. Insulin secretion was determined as the acute insulin response to glucose (AIRg) during the first 10 min of a frequently sampled intravenous glucose tolerance test. Where noted, data were adjusted for baseline values and background antidiabetes medication.

**Results:** An adjusted mean increase from baseline in GDR (last observation carried forward), at Week 12, was observed with dapagliflozin (7.98%) versus a decrease with placebo (-9.99%). The 19.97% (95% confidence interval 5.75–36.10) difference in GDR versus placebo was statistically significant ( $P = 0.0059$ ). A change from baseline in adjusted mean AIRg of 15.39mU/L min was observed with dapagliflozin at Week 12, versus -12.73mU/L min with placebo ( $P = 0.0598$ ). Over 12 weeks, numerical reductions from baseline in glycosylated hemoglobin (HbA1c), fasting plasma glucose, and body weight were observed with dapagliflozin (-0.38%, -0.39 mmol/L, and -1.58%, respectively) versus slight numerical increases with placebo (0.03%, 0.26 mmol/L, and 0.62%, respectively).

**Conclusions:** In patients with T2DM and inadequate glycemic control, dapagliflozin treatment improved insulin sensitivity in the setting of reductions in HbA1c and weight.

#### Editor's comment

This study evaluated the effect of dapagliflozin over 12 weeks on glucose disappearance rate (GDR) and acute insulin response to glucose (AIRg) and integrates the effects of weight loss with those of a reduction in glucotoxicity. Thus, while evaluating the overall effect of this treatment, it is not possible to delineate the relative contribution of improvement from reduction in glucose toxicity, weight loss, or other aspects of improvement in overall metabolic profile.

Thus the improvement in glycemic parameters and reduction in body weight due to SGLT-2 inhibition by dapagliflozin are associated with improvement in insulin sensitivity.



## First-Trimester Maternal Abdominal Adiposity Predicts Dysglycemia and Gestational

### Diabetes Mellitus in Midpregnancy.

Leanne R. De Souza et al. *Diabetes Care* Publish Ahead of Print, published online November 23, 2015.

This study assessed the association between first-trimester abdominal adiposity and dysglycemia and gestational diabetes mellitus (GDM) in mid pregnancy. In a prospective cohort of 485 women, Leanne R. De Souza et al measured subcutaneous (SAT), visceral (VAT), and total (TAT) adipose tissue depth, using ultrasound at 11–14 weeks' gestation. Logistic regression analysis assessed the relation between quartiles of SAT, VAT, or TAT depth and the composite outcome of impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or GDM, based on a 75-g oral glucose tolerance test at 24–28 weeks.

Adjusting for maternal age, ethnicity, family history of diabetes, and BMI, quartile 4 versus quartile 1 VAT (adjusted odds ratio [aOR] 3.1, 95% CI 1.1–9.5) and TAT (aOR 2.7, 95% CI 1.1–7.8) were significantly associated with the composite outcome, but SAT was not (aOR 1.8, 95% CI 0.70–4.8). The same was seen for GDM alone. Elevated first-trimester VAT and TAT depth independently predicted the risk of dysglycemia later in pregnancy.

#### Editor's comment

**This study demonstrated that Total Adipose Tissue, and especially VAT, appear to be important pathogenic markers of abnormal glucose homeostasis and GDM in pregnancy. SAT alone appeared less important, however. SAT has a heterogeneous histology, with two distinct deep and superficial layers, of which the former inhibits metabolic activity like that of VAT. Certainly, future work should attempt to distinguish deep and superficial SAT layers.**

**Ultrasound measurement of maternal abdominal adiposity affords the opportunity to overcome some of the limitations posed by using BMI. This proposed screening approach uses a practical and validated ultrasound based first-trimester screening tool.**

**Using this tool and identifying women with high VAT or TAT might enable a practitioner to mitigate the onset of GDM through the upstream management of risk factors. This approach can be compared with our current downstream approach of screening and treating GDM in the second trimester of pregnancy.**

## Acute Kidney Injury Predicts Major Adverse Outcomes in Diabetes: Synergic Impact With Low Glomerular Filtration Rate and Albuminuria

Mathilde Monseu et al. *Diabetes Care* 2015;38:2333–2340 | DOI: 10.2337/dc15-1222

Subjects with diabetes are prone to the development of cardiovascular and non-cardiovascular complications. In separate studies, acute kidney injury (AKI), albuminuria, and low estimated glomerular filtration rate (eGFR) were shown to predict adverse outcomes, but, when considered together, their respective prognostic value is unknown. Patients with type 2 diabetes consecutively recruited in the SURDIAGENE cohort were prospectively followed up for major diabetes-related events, as adjudicated by an independent committee: death (with cause), major cardiovascular events (myocardial infarction, stroke, congestive heart failure, amputation, and arterial revascularization), and renal failure (i.e., sustained doubling of serum creatinine level or end-stage renal disease).

Intra-hospital AKI occurred in 411 of 1,371 patients during the median follow-up period of 69 months. In multivariate analyses, AKI was significantly associated with cardiovascular and non-cardiovascular death, including cancer-related death. In multivariate analyses, AKI was a powerful predictor of major adverse cardiovascular events, heart failure requiring hospitalization, myocardial infarction, stroke, lower-limb amputation or revascularization, and carotid artery

revascularization. AKI, eGFR, and albuminuria, even when simultaneously considered in multivariate models, predicted all-cause and cardiovascular deaths. All three renal biomarkers were also prognostic of most adverse outcomes and of the risk of renal failure. AKI, low eGFR, and elevated albuminuria, separately or together, are compelling biomarkers of major adverse outcomes and death in diabetes.

**Editor's comment**

**The current study is probably the first one to examine the risk for death, cardiovascular events, and noncardiovascular events in a comprehensive way in relation to AKI, albuminuria, and eGFR, considered separately or together, and the first one evaluating the long-term risk of AKI in consecutively recruited patients with diabetes.**

**AKI is a powerful predictor of major cerebrovascular, cardiovascular and noncardiovascular events and deaths in individuals with type 2 diabetes. All three renal markers (AKI, eGFR, and albuminuria) alone or considered together are synergistically predictors of total and cardiovascular deaths, and renal outcomes.**

### Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman et al. for the EMPA-REG OUTCOME Investigators. Published on September 17, 2015, at NEJM.org. DOI: 10.1056/NEJMoa1504720

The effects of empagliflozin, an inhibitor of sodium–glucose cotransporter 2, in addition to standard care, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high cardiovascular risk are not known.

The study group randomly assigned patients to receive 10 mg or 25 mg of empagliflozin or placebo once daily. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, as analyzed in the pooled empagliflozin group versus the placebo group. The key secondary composite outcome was the primary outcome plus hospitalization for unstable angina.

A total of 7020 patients were treated (median observation time, 3.1 years). The primary outcome occurred in 490 of 4687 patients (10.5%) in the pooled empagliflozin group and in 282 of 2333 patients (12.1%) in the placebo group (hazard ratio in the empagliflozin group, 0.86; 95.02% confidence interval, 0.74 to 0.99;  $P = 0.04$  for superiority). There were no significant between-group differences in the rates of myocardial infarction or stroke, but in the empagliflozin group there were significantly lower rates of death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction), hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction), and death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction). There was no significant between-group difference in the key secondary outcome ( $P = 0.08$  for superiority). Among patients receiving empagliflozin, there was an increased rate of genital infection but no increase in other adverse events.

EMPA-REG OUTCOME ClinicalTrials.gov number, NCT01131676.)

**Editor's comment**

**Patients with type 2 diabetes are usually at high risk for cardiovascular events. In this trial, patients with type 2 diabetes at high risk for cardiovascular events who received empagliflozin had significantly lower rates of the primary composite cardiovascular outcome and of death from any cause than did those in the placebo group when the study drugs were added to standard care. This is the first antidiabetic drug to establish its efficacy as cardioprotective advantage .**