Dietary Marine ω-3 Fatty Acids and Incident Sight-Threatening Retinopathy in Middle-Aged and Older Individuals With Type 2 Diabetes: Prospective Investigation From the PREDIMED Trial for the Prevención con Dieta Mediterránea (PREDIMED) Investigators.

Sala-Vila A, Díaz-López A, Valls-Pedret C, et al;. JAMA Ophthalmol. 2016. doi:10.1001/jamaophthalmol.2016.2906.

This Spanish study finds that those who ate 2 servings of fatty fish per week were 48 per cent less likely to develop diabetic retinopathy and may be enough to lower the heightened risk for blindness that those with diabetes face.

Diabetic retinopathy is a serious complication of type 2 diabetes is the most frequent cause of diabetes-related blindness. The study group analysed whether regular consumption of seafood, fatty fish in particular in the absence of any advice to increase seafood consumption or fish oil supplementation decreased the risk of diabetic retinopathy. From Barcelona the group led by Sala-Vila focused on patients whose overall diet was already composed of mostly low-fat or plant-based foods. They found that, those who consumed at least two servings of fatty fish weekly had a lower risk for diabetic retinopathy than those whose diets included less fish or no fish.

Study participants were with type 2 diabetes and divided into three different groups, as per assignment of a different diet. The first followed a low-fat diet. The second followed a Mediterranean (plant-based/red meat-free) diet, supplemented with extra virgin olive oil. And the third also followed a Mediterranean diet, supplemented by 30 grams a day of omega-3 rich walnuts, hazelnuts, and almonds. That study found it was those in the second group who saw their vision risks fall.

Working with the same pool of participants, they were asked about 3,600 diabetic men and women between the ages of 55 and 80 to report how often they consumed eight types of seafood before embarking on their assigned diets. Once on their diets, Sala-Vila's team tracked seafood consumption habits for nearly five years. They found that those who routinely consumed 500 milligrams (mg) a day of omega-3 fatty acid in their diets (equal to two servings of fatty fish per week) were 48 percent less likely to develop diabetic retinopathy than those who consumed less. This may be explained by the drop in systemic inflammation that occurs as overall omega-3 levels go up.

But it is not clear that whether diabetics might realize even more protection by further increasing fatty fish consumption. It is not also clear whether the omega-3 supplements do the trick as well as eating fish did.

1. Editor's Comment

Fish oil supplements appear to be safe, but probably omega-3 rich foods are much better.

One should always try to include omega-3 rich foods in their daily diet, as supplements rarely make up for a poor underlying diet. Also, the foods rich in omega-3 are also rich in other key nutrients such as vitamin E and protein that promote health.

We are convinced about the effects of omega-3 fatty acids on cardiovascular diseases, but this is a new study showing salutary effect on retinopathy.

Statin Therapy Prevents the Onset of Parkinson Disease in Patients with Diabetes;

Lin K, Yang C, Lee M, Ho S, Liu C, Shin S; Annals of Neurology (Jul 2016)

Lin K et al studied the association between the statin dosage and the risk of Parkinson disease (PD) in diabetic patients in Taiwan. One million patients were randomly sampled from a National Health Insurance (NHI) database and followed from 2001-2008. Diabetic patients were screened by diagnosis of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, and statin dosage was determined according to the NHI pharmacy database. Parkinson Disease (PD) was diagnosed on the basis of ICD-9-CM codes and anti-Parkinson medication use. Statin users was classified by statin dose-duration-day (DDD) > 28 and matched with non-users of statins using coarsened exact matching (CEM) method. There were 50432 patients and half of them were statin users. They examined the risk of PD between statin users and non-users of statins and further tested the trends of the relative risk between the statin dosage and PD.

The PD incidence rate was lower in statin users than in non-users of statins. The crude hazard ratio (HR) of PD incidence in statin users was 0.65 (0.57-0.74) in female and 0.60 (0.51-0.69) in male compared with non-users of statins. After Cox-regression analysis, all statins except lovastatin exerted protective effects on PD incidence and had a significant dose-dependent trend.

2. Editor's Comment

In Taiwanese diabetic patients, the risk of Parkinson disease (PD) is lower in statin users than in non-users of statins. Statin users, except lovastatin users, are dose-dependently associated with a decreased incidence of PD compared with non-users of statins.

We know about the effects of statins on the brain in terms of cerebrovascular accidents and cognitive function. This finding provides a new indication for statin beyond lipid control and vascular events in diabetic patients.

OCT1, SERT Genes Play Role in Metformin Intolerance

Tanja Dujic, etal. published online Aug. 4 in Diabetes Care.

Intolerance up with low-expressing SERT S* alleles; multiplicative interaction for OCT1, SERT genotypes

The interaction between the organic cation transporter 1 and the serotonin reuptake transporter seems to play a role in metformin intolerance,

according to a study published online Aug. 4 in Diabetes Care.

Tanja Dujic and colleagues from Sarajevo in Bosnia and Herzegovina, examined the correlation between a common polymorphism in the SERT gene and metformin gastrointestinal intolerance. The effect of composite SERT 5-HTTLPR/rs 25531 genotypes L*L*, L*S*, and S*S* was explored in 1,356 fully-tolerant and 164 extreme metformin-intolerant patients.

The researchers found that the odds of metformin intolerance were increased with the number of low-expressing SERT S* alleles (odds ratio, 1.31). There was a multiplicative interaction between OCT1 and SERT genotypes (P=0.003). In patients carrying L*L* genotype, the presence of two deficient OCT1 alleles correlated with more than nine-fold increased odds of metformin intolerance in analyses stratified by SERT genotype (odds ratio, 9.25); a much smaller effect was seen in L*S* carriers and no effect was seen in S*S* carriers.

"Further studies are needed to replicate these findings and to substantiate the hypothesis that metformin gastrointestinal side effects could be related to the reduced intestinal serotonin uptake," the authors write.

3. Editor's Comment

Pharmacogenomics are in the phase of strong development. Genetics of metformin intolerance are identified. The interaction between the organic cation transporter 1 (OCT1) and the serotonin reuptake transporter (SERT) seems to play a role in metformin intolerance.This will prevent the use of metformin in intolerant patients and gives relief from unnecessary harassment.

Cardiovascular Safety of Empagliflozin in Patients With Type 2 Diabetes: A Meta-Analysis of Data From Randomized Placebo-Controlled Trials.

A Salsali, G Kim, HJ Woerle, UC Broedl, S Hantel. Diabetes Obes Metab 2016 Jul 04; [EPub Ahead of Print],

This study assessed the effect of empagliflozin on cardiovascular (CV) risk in patients with type 2 diabetes (T2DM) through a meta-analysis of data from 8 placebo-controlled trials. Data were analysed from 8 randomized placebo-controlled trials undertaken to investigate the efficacy and safety of empagliflozin 10 mg and 25 mg once daily in patients with T2DM, comprising patients at low/medium and high CV risk.

Suspected CV events were prospectively adjudicated. The empagliflozin 10 mg and 25 mg groups were pooled for the primary analysis. The primary endpoint was a composite of CV death, non-fatal myocardial infarction (MI), non-fatal stroke, and hospitalization for unstable angina (4-point major adverse CV events [MACE]). The secondary endpoint was a composite of CV death, non-fatal MI, and non-fatal stroke (3-point MACE). Risk estimates were calculated using Cox regression analysis.

A total of 3835 patients received placebo and 7457 received empagliflozin. Total exposure was 7448.3 years for placebo and 15482.1 years for empagliflozin. Four-point MACE occurred in 365 (9.5%) patients receiving placebo and 635 (8.5%) receiving empagliflozin (hazard ratio for empagliflozin versus placebo 0.86 [95% CI 0.76, 0.98]). Three-point MACE occurred in 307 (8.0%) patients receiving placebo and 522 (7.0%) receiving empagliflozin (hazard ratio for empagliflozin versus placebo 0.84 [95% CI 0.73, 0.96]).

In a meta-analysis of data from 8 randomized trials involving 11292 patients with T2DM at low/medium or high CV risk, empagliflozin was associated with a reduced risk of 4-point MACE and 3-point MACE compared with placebo.

4. Editor's Comment

In EMPAREG trial, cardiovascular protection was seen in people with diabetes with high risk cardiovascular disease. This meta-analysis shows the same outcome in low/medium cardiovascular risk patients also.

Greater Drop in Hemoglobin A1c With Empagliflozin + Metformin

Samy Hadjadj et al. published online Aug. 4 in Diabetes Care 2016

Twenty-four weeks of empagliflozin + metformin correlates with a significantly greater reduction in hemoglobin A1c compared with once-daily empagliflozin or twice-daily metformin, according to this study published in Diabetes Care.

Twenty-four weeks of empagliflozin + metformin correlates with a significantly greater reduction in hemoglobin A1c (HbA1c) compared with once-daily empagliflozin or twice-daily metformin.

Samy Hadjadj et al randomized 1,364 drug-naive patients with type 2 diabetes to empagliflozin + metformin, empagliflozin, or metformin for 24 weeks. The authors examined the change from baseline in HbA1c at week 24. At week 24, they observed reductions in HbA1c of −1.9 to −2.1 percent with empagliflozin + metformin twice-daily regimens; −1.4 percent with empagliflozin once-daily regimens; and −1.2 to −1.8 percent with metformin twice-daily regimens. Empagliflozin + metformin twice-daily regimens correlated with significantly greater reductions in HbA1c than for empagliflozin once-daily regimens ($P < 0.001$) and metformin twice-daily regimens ($P < 0.01$). Compared with metformin twice-daily regimens, empagliflozin + metformin twice-daily regimens correlated with significantly greater weight loss at week 24 (all $P < 0.001$). Across the groups, adverse event rates were similar.

5. Editor's Comment

Initial combinations of empagliflozin + metformin for 24 weeks significantly reduced HbA1c vs. empagliflozin once daily and metformin twice daily, without increased hypoglycaemia, reduced weight vs. metformin twice daily, and were well tolerated. Both drugs acting on different target organs are also another advantage in achieving quick control.

Sleep: Implications of Interrupted, Insufficient Sleep on Metabolism, Obesity, Type 2 Diabetes Risk, Glucose Management.

Hammond T. F02 - Presented at: AADE 2016; August 12-15, 2016; San Diego, CA

Better sleep may improve diabetes outcomes. Regulating and maintaining healthy sleep habits may be key to successful management of diabetes. Consequently, greater emphasis should be placed on helping patients achieve optimal sleep, according to the study by Terese Hammond presented at the American Association of Diabetes Educators (AADE) 2016 Annual Meeting.

There are several reasons for endocrinologists to care about sufficient, high-quality sleep. Foremost is the observation that sleep conditions such as obstructive sleep apnea and insomnia are highly prevalent amongst diabetics. Actually sleep matters much more than may be appreciated. Too little (less than 7 hours) or too much (more than 9 hours) are associated with a host of negative health outcomes. Further, insufficient sleep has a profound effect on obesity, energy expenditure, and caloric intake, especially carbohydrate intake.

The metabolic milieu that is created when adults consistently sleep less than 7 hours per night is highly inflammatory and creates a low-leptin, high-ghrelin, high-cortisol, high-glucose environment that perpetuates insulin resistance and beta-cell dysfunction. Awareness of the importance and long-term positive health implications of adequate sleep among both endocrinologists and the patients they treat is low-hanging fruit in the journey to adequate glycemic control, optimization of chronic medical disease care, and overall wellness.

Behavioural interventions to address insufficient sleep can positively affect sleep duration and long-term health outcomes. For instance, cognitive behavioural therapy can be used effectively to restore optimal levels of sleep. Additionally, there are a variety of online resources for cognitive behavioural therapy that can be accessed by endocrinologists and their patients. Dr Hammond said endocrinologists can significantly increase awareness among their patients by merely providing a good handout on sleep hygiene. She recommends information found at the National Sleep Foundation's website.

Quality sleep is an essential component of metabolic health. Metabolism is meant to be a zero sum game, with energy expenditure consistently balancing energy intake, and poor sleep is a potent indicator that your patient with diabetes is not optimizing their metabolic health.

Dr Hammond pointed out that recognition of sleep complaints, either through direct questioning or through the use of simple screening tools during routine visits, can raise awareness of the importance of sleep among both providers and patients. Simple, but far from easy, behavioral changes, explained Dr Hammond, can yield substantial long-term improvements in glycemic control, cardiovascular risk, and subjective and objective quality of life.

6. Editor's Comment

Treatment of prevalent sleep disorders such as obstructive sleep apnea have significant implications for control of diabetes and are directly associated with conditions such as fatty liver, metabolic syndrome, and cognitive decline and impairment. When control is difficult to achieve one should enquire for sleep disturbances. Do not ignore sleep symptoms or harbour false beliefs that poor sleep is only a symptom of other diseases. Treatment of primary sleep disorders is often highly effective, and appropriate referral to sleep specialists can have dramatic results in the patients' health and wellness.

Pioglitazone Prevents Diabetes in Insulin-Resistant Patients With Cerebrovascular Disease

Diabetes Care 2016 Jul 27; [EPub Ahead of Print], SE Inzucchi, CM Viscoli, LH Young, KL Furie, M Gorman, AM Lovejoy, S Dagogo-Jack, F Ismail-Beigi, MT Korytkowski, RE Pratley, GG Schwartz, WN Kernan

This study shows that, pioglitazone prevents diabetes in insulin-resistant patients with cerebrovascular disease

The IRIS (Insulin Resistance Intervention after Stroke) trial documented two important findings: (1) secondary prevention of stroke/myocardial infarction

(MI) by 24% in nondiabetic patients presenting with ischemic stroke/TIA and insulin resistance, when pioglitazone was added instead of placebo, and (2) prevention of diabetes by 51% in the insulin-resistant stroke patients receiving pioglitazone. The mechanisms by which pioglitazone improved cardiovascular (CV) outcomes in the IRIS trial remain uncertain. It seems very unlikely that the small changes in glucose levels have contributed to the significant risk reduction of CV events; however, pioglitazone demonstrated several other benefits beyond glucose control including lowering of blood pressure and chronic inflammation and increasing HDL cholesterol, each of which might have contributed to the risk reduction.

The findings of the IRIS study are in line with the secondary prevention of stroke and myocardial infarction by 47% and 28%, respectively, observed in the PROactive study when patients with type 2 diabetes were randomized to pioglitazone. The IRIS study is the first to show prevention of diabetes in insulin-resistant patients with a history of stroke; however, the clinically relevant effects are in line with the well established diabetes prevention effect of pioglitazone in patients with pre diabetes, oberved in ACT Now and other studies. Weight gain and the increased risk for heart failure (not seen in IRIS, since only 14% had a history of MI in contrast to 50% of the diabetic patients in PROactive) and bone fractures will limit the future use of pioglitazone in patients with high CV risk despite the very positive effects on the future risk for CV disease and diabetes development.

The Insulin Resistance Intervention after Stroke (IRIS) trial recently found that pioglitazone reduced risk for stroke and myocardial infarction in nondiabetic, insulin-resistant patients with a recent ischemic stroke or transient ischemic attack (TIA). This report provides detailed results on the metabolic effects of pioglitazone and the trial's prespecified secondary aim of diabetes prevention.

A total of 3,876 patients with recent ischemic stroke or TIA, no history of diabetes, fasting plasma glucose (FPG) <126 mg/dL, and insulin resistance by homeostasis model assessment of insulin resistance (HOMA-IR) score >3.0 were randomly assigned to pioglitazone or placebo. Surveillance for diabetes onset during the trial was accomplished by periodic interviews and annual FPG testing.

At baseline, the mean FPG, HbA1c, insulin, and HOMA-IR were 98.2 mg/dL (5.46 mmol/L), 5.8% (40 mmol/mol), 22.4 μ IU/mL, and 5.4, respectively. After 1 year, mean HOMA-IR and FPG decreased to 4.1 and 95.1 mg/dL (5.28 mmol/L) in the pioglitazone group and rose to 5.7 and 99.7 mg/dL (5.54 mmol/L), in the placebo group (all $P < 0.0001$). Over a median follow-up of 4.8 years, diabetes developed in 73 (3.8%) participants assigned to pioglitazone compared with 149 (7.7%) assigned to placebo (hazard ratio, 0.48 [95% CI 0.33-0.69]; $P < 0.0001$). This effect was predominately driven by those with initial impaired fasting glucose (FPG >100 mg/dL [5.6 mmol/L]; HR 0.41 [95% CI 0.30-0.57]) or elevated HbA1c (>5.7% [39 mmol/mol]; HR 0.46 [0.34-0.62]).

Among insulin-resistant but non-diabetic patients with a recent ischemic stroke or TIA, pioglitazone decreased the risk of diabetes while also reducing the risk of subsequent ischemic events. Pioglitazone is the first medication shown to prevent both progression to diabetes and major cardiovascular events as prespecified outcomes in a single trial.

7. Editor's Comment

In this study, patients who suffered a recent stroke or transient ischaemic attack (TIA) without diabetes, but with confirmed insulin resistance, were randomised to receive pioglitazone or placebo.

After 1 year of follow-up, fasting plasma glucose and the HOMA-IR score had decreased significantly in the pioglitazone group but increased significantly in those taking the placebo. After a median of 4.8 years of follow-up, 3.8% of the pioglitazone group were diagnosed with diabetes vs. 7.7% of the placebo group.

This effect was particularly seen in patients with an impaired fasting plasma glucose or elevated HbA1c at baseline.

In patients with a recent stroke or TIA and insulin resistance, pioglitazone significantly reduces the risk of progression to diabetes.

This study establishes the extraglycaemic benefits of the drug.

Dapagliflozin as Additional Treatment to Liraglutide and Insulin in Patients With Type 1 Diabetes

J. Clin. Endocrinol. Metab. 2016 Aug 04; [EPub Ahead of Print], ND Kuhadiya, H Ghanim, A Mehta, M Garg, S Khan, J Hejna, B Torre, A Makdissi, A Chaudhuri, M Batra, P Dandona

Use of dapagliflozin in type 1 diabetes is still off label indication. But this study shows that dapagliflozin added to liraglutide and insulin improves glycemia and weight loss in type 1 diabetes

SGLT-2 inhbitors increase glucagon, which promotes lipolysis and fat oxidation, increasing ketone body formation. This is believed to contribute to the increased risk of diabetic ketoacidosis seen with these drugs. This interesting study addresses the question of whether concomitant use of liraglutide, a GLP-1 agonist that putatively suppresses glucagon, would mitigate this effect in patients with type 1 diabetes. Surprisingly, despite liraglutide treatment, SGLT-2 inhibitor use was associated with an increase in glucagon and ketone body formation. Moreover, in this small study, two subjects developed diabetic ketoacidosis. These results highlight the potential risk of SGLT-2 inhibitor use in patients with type 1 diabetes and demonstrate that this risk does not seem to be diminished with a GLP-1 receptor agonist. Consequently, SGLT-2 inhibitors cannot be routinely recommended as adjunctive therapy in patients with type 1 diabetes at this point.

It is imperative that novel approaches to treatment of type 1 diabetes (T1D) are devised.

The objective of the study was to investigate whether addition of dapagliflozin to insulin and liraglutide results in a significant reduction in glycemia and body weight.

This was a randomized clinical trial conducted at a single academic medical center. The participants included T1D patients on liraglutide therapy for at least last 6 months. Thirty T1D patients were randomized (in 2:1 ratio) to receive either dapagliflozin 10 mg or placebo daily for 12 weeks.

Main outcome measure was the change in mean glycated hemoglobin after 12 weeks of dapagliflozin when compared with placebo was measured.

In the dapagliflozin group, glycated hemoglobin fell by 0.66% ± 0.08% from 7.8% ± 0.21% ($P < .01$ vs placebo), whereas it did not change significantly in the placebo group from 7.40% ± 0.20% to 7.30% ± 0.20%. The body weight fell by1.9 ± 0.54kg ($P < .05$ vs placebo). There was no additional hypoglycemia (blood glucose < 3.88 mmol/L; $P = .52$ vs placebo). In the dapagliflozin group, there were significant increases in the plasma concentrations of glucagon by 35% ± 13% ($P < .05$), hormone-sensitive lipase by 29% ± 11% ($P < .05$), free fatty acids by 74% ± 32% ($P < .05$), acetoacetate by 67% ± 34% ($P < .05$), and β-hydroxybutyrate by 254% ± 81% ($P < .05$). Urinary ketone levels also increased significantly ($P < .05$). None of these changes was observed in the placebo group. Two patients in the dapagliflozin group developed diabetic ketoacidosis.

Addition of dapagliflozin to insulin and liraglutide in patients with T1D results in a significant improvement in glycemia and weight loss while

increasing ketosis. If it is decided to use this approach, then it must be used only by a knowledgeable patient along with an endocrinologist who is well versed with it.

8. Editor's Comment

This study of 30 patients looked at novel treatment methods for patients with type 1 diabetes. Two randomised groups (2:1 ratio) were administered dapagliflozin (10 mg) vs. placebo daily over 12 weeks.

In patients randomised to dapagliflozin, levels of glycated haemoglobin and body weight were reduced ($P < 0.01$ and $P < 0.05$, respectively), and there was no increase in hypoglycaemia ($P = 0.52$). Significant changes included an increase in urinary ketones ($P < 0.05$). Of the patients receiving dapagliflozin, two developed diabetic ketoacidosis.

Supplementing insulin and liraglutide with dapagliflozin significantly reduced glycaemia and body weight in diabetic patients.

Clinical manifestations of kidney disease among US adults with diabetes, Afkarian M, Zelnick LR, Hall YN, et al. 1988-2014. JAMA.

2016; 316 (6): 602-610. doi:10.1001/jama.2016.10924.

From 1988 to 2014 there was no change in the overall prevalence of diabetic kidney disease, according to a study published in the Journal of the American Medical Association.

Maryam Afkarian, from the University of Washington in Seattle, and colleagues characterized the clinical manifestations of kidney disease among U.S. adults with diabetes. Data were obtained from 6251 adults aged 20 years and older with diabetes mellitus participating in the National Health and Nutrition Examination Surveys from 1988 through 2014.

The researchers observed no change over time in the prevalence of any diabetic kidney disease, defined as persistent albuminuria, persistent reduced estimated glomerular filtration rate (eGFR), or both (prevalence ratio, 0.95; 95% confidence interval [CI], 0.86 to 1.06, after adjustment for age, sex, and race/ethnicity). There was a decrease in the prevalence of albuminuria over time (adjusted prevalence ratio, 0.76; 95% CI, 0.65 to 0.89). The prevalence of reduced eGFR increased over time (adjusted prevalence ratio, 1.61; 95% CI, 1.33 to 1.95), and a similar pattern was seen for severely reduced eGFR (adjusted prevalence ratio, 2.86; 95% CI, 1.38 to 5.91).

Among U.S. adults with diabetes from 1988 to 2014, the overall prevalence of diabetic kidney disease did not change significantly, whereas the prevalence of albuminuria declined and the prevalence of reduced eGFR increased.

9. Editor's Comment

This is the most frustrating news that with so much efforts and researches there is no improvement in overall prevalence of diabetic kidney diseases. The study group found no change over time in the prevalence of any diabetic kidney disease, defined as persistent albuminuria, persistent reduced estimated glomerular filtration rate (eGFR) or both after adjustment for age, sex, and race/ethnicity.

Standardized Mixed-Meal Tolerance and Arginine Stimulation Tests Provide Reproducible and Complementary Measures of β-cell Function: Results From the Foundation for the National Institutes of Health Biomarkers Consortium Investigative Series.

Shankar SS, Vella A, Raymond RH, et al; for the the Foundation for the National Institutes of Health β-Cell Project Team. Diabetes Care. 2016. doi:10.2337/dc15-0931.

Standardized mixed-meal tolerance tests (MMTT) and arginine stimulation tests (AST) provide reproducible measures of beta-cell function across glucose tolerance states, according to a study published in Diabetes Care.

Sudha S. Shankar and colleagues characterized the responses to, and reproducibility of, standardized methods of in vivo beta-cell function. Participants with normal glucose tolerance (23 participants), prediabetes (7 participants), and type 2 diabetes (22 participants) underwent 2 standardized MMTT, 2 standardized AST, and 1 frequently sampled intravenous glucose tolerance test (FSIGT).

The researchers found that from the MMTT, insulin secretion in type 2 diabetes was more than 86% lower than in normal glucose tolerance or prediabetes. There was a decrease in insulin sensitivity from normal glucose tolerance to prediabetes (about 50%) to type 2 diabetes (93% lower).

At basal glucose and during hyperglycemia, insulin secretory response to arginine was lower in type 2 diabetes compared with normal glucose tolerance and prediabetes in the AST. FSIGT showed decreases across populations in both insulin secretion and insulin sensitivity; no significant difference was observed in insulin sensitivity for prediabetes and type 2 diabetes populations.

10. Editor's Comment

To asses the beta cell function, reproducibility was generally good for the MMTT and very good for the AST.

Standardised MMTT and AST provide reproducible and complementary measures of beta-cell function with characteristics favourable for longitudinal interventional trial uses.

Genome-wide association study of the modified Stumvoll Insulin Sensitivity Index identifies BCL2 and FAM19A2 as novel insulin sensitivity loci.

Walford GA, Gustafsson S, Rybin D, et al. Diabetes. 2016. doi:10.2337/db16-0199.

Two novel loci have been identified that are associated with insulin sensitivity, according to a study published in Diabetes. Geoffrey A. Walford, from Boston, and colleagues performed a genome-wide association study of the modified Stumvoll Insulin Sensitivity Index (ISI) within the Meta-Analyses of Glucose and Insulin-related traits Consortium.

Discovery was performed in 16 753 individuals, and the authors attempted replication in 13 354 independent individuals for the 23 most significant novel loci. The correlation with ISI was assessed in different models.

The researchers found that in a model analyzing the combined influence of genotype effect adjusted for BMI and the interaction effect between the

genotype and BMI, 3 variants reached genome-wide significance: rs13422522 (NYAP2), rs12454712 (BCL2), and rs10506418 (FAM19A2). Conditioning on the known IRS1 insulin sensitivity locus eliminated the association at NYAP2; the associations atBCL2 and FAM19A2 were independent of known cardio-metabolic loci.

11. Editor's Comment

The researchers have identified two novel loci and replicated known variants associated with insulin sensitivity. Further studies are needed to clarify the causal variant and function at the *BCL2* and *FAM 19A2* loci.

Association of accelerometer-assessed sedentary behavior with diabetic retinopathy in the United States. Loprinzi L.

JAMA Ophthalmol. 2016; doi: 10.1001/jamaophthalmol.2016.2400.

Sedentary behavior (SB) seems to be associated with diabetic retinopathy (DR), according to a research letter published in JAMA Ophthalmology. Paul D. Loprinzi, examined the correlation between SB and DR using data from the 2005 to 2006 National Health and Nutrition Examination Survey. Data were analyzed for 282 participants with diabetes.

Loprinzi found that after adjustment for confounding variables, a 60-minute/day increase in SB correlated with an increase in the odds of having mild or worse DR (odds ratio [OR], 1.16; 95% confidence interval [CI], 1.00 to 1.35; P=.04). There was no correlation for total physical activity with DR (OR, 1.00; 95% CI, 0.99 to 1.01; P=.36). SB remained associated with DR even after adjustment for duration of diabetes (OR, 1.29; 95% CI, 1.04 to 1.60; P=.02). There was no evidence for a multiplicative effect of SB and physical activity on DR (OR, 1.00; 95% CI, 0.99 to 1.01; P=.89).

12. Editor's Comment

The plausibility of this positive association between sedentary behaviour and diabetic retinopathy (DR) may in part be a result of the increased cardiovascular disease risks associated with SB, which in turn may increase the risk of DR,This association does not prove a cause and effect of sedentary behaviour and increased chance of worsening DR.

Effects of Vitamin D Supplementation on HbA1c and Fasting Glucose in Hypertensive Patients: A Randomized Controlled Trial

MR Grübler, M Gaksch, K Kienreich, N Verheyen, J Schmid, BÓ Hartaigh, G Richtig, H Scharnagl, A Meinitzer, A Fahrleitner-Pammer, W März, A Tomaschitz, S Pilz. Diabetes Obes Metab 2016 Jun 23; [EPub Ahead of Print],

Experimental data have indicated that vitamin D insufficiency has an important influence on glucose metabolism. The majority of epidemiological studies have demonstrated an association between

low vitamin D and insulin resistance and/or type 2 diabetes mellitus. Nevertheless evidence from randomized controlled trials remains inconclusive.

This study investigated the efficacy of vitamin D supplementation on glycaemic control.

The Styrian Vitamin D Hypertension Trial is a single-centre, double-blind, placebo-controlled study conducted between 2011 and 2014 at the Medical University of Graz, Austria. They enrolled 200 persons with arterial hypertension and 25-hydroxyvitamin D (25 (OH) D) concentrations below 30 ng/mL. Study participants were randomized to receive either 2800 IU of vitamin D or placebo per day for 8 weeks. The present investigation is a post-hoc analysis that incorporated analysis of covariance (ANCOVA) approach while adjusting for baseline differences.

A total of 185 participants (mean ± SD age, 60.1 ± 11.3 years; 47% women; mean 25 - hydroxyvitamin D, 21.2 ± 5.6 ng/mL, mean HbA1c 44.8 ± 11.8 mmol/mol and mean BMI 30.4 ± 5.4 kg/m (2)) completed the trial. ANCOVA revealed a mean treatment effect (95% confidence interval) on HbA1c of -3.52 mmol/mol (95% CI -6.7 to -0.34; P = 0.045). There was no difference in fasting glucose -4.7 mg/dL (95% CI -16.3 to 6.9; P = 0.426).

Vitamin D supplementation in obese hypertensive patients with low 25-hydroxyvitamin D reduces HbA1c. This finding warrants further investigations on potential vitamin D effects on glucose homeostasis.

13. Editor's Comment

In this randomised controlled trial, investigators evaluated the efficacy of vitamin D supplementation on glycaemic control in 185 participants with arterial hypertension and low 25-hydroxyvitamin D concentrations.

Participants receiving vitamin D had reduced HbA1c compared with those receiving placebo (difference of −3.52 mmol/mol; P = 0.045) but no change in fasting glucose (−4.7 mg/dL; P = 0.426).

Among individuals with arterial hypertension, vitamin D supplementation reduced HbA1c.

Involvement of Glucagon-Like Peptide-1 in the Glucose-Lowering Effect of Metformin.

E Bahne, M Hansen, A Brønden, DP Sonne, T Vilsbøll, FK Knop .Diabetes Obes Metab 2016 Jul 13; [EPub Ahead of Print

Metformin is an oral antihyperglycaemic drug used in the first-line treatment of type 2 diabetes. Metformin's classic and most well-known blood glucose-lowering mechanisms include reduction of hepatic gluconeogenesis and increased peripheral insulin sensitivity. Interestingly, intravenously administered metformin is ineffective and recently, metformin was shown to increase plasma concentrations of the glucose-lowering gut in cretin hormone glucagon-like peptide-1 (GLP-1), which may contribute to metformin's glucose-lowering effect in patients with type 2 diabetes. The mechanisms behind metformin-induced increments in GLP-1 levels remain unknown, but it has been hypothesized that metformin stimulates GLP-1 secretion directly and/or indirectly and that metformin prolongs the half-life of GLP-1. Also, it has been suggested that metformin may potentiate the glucose-lowering effects of GLP-1 by increasing target tissue sensitivity to GLP-1. The present article

critically reviews the possible mechanisms by which metformin may affect GLP-1 levels and sensitivity and discusses whether such alterations may constitute important and clinically relevant glucose-lowering actions of metformin.

14. Editor's Comment

Metformin works by a variety of blood glucose–lowering mechanisms, one of which may involve increasing plasma concentrations of GLP-1. This review summarises the evidence for the possible mechanisms by which metformin improves GLP-1 levels, including direct and indirect actions.

The antihyperglycaemic mechanisms of metformin remain unclear, but evidence is mounting that GLP-1 modulation contributes to the overall antidiabetic effect of the drug.

Sucralose Promotes Food Intake Through NPY and a Neuronal Fasting Response

QP Wang, YQ Lin, L Zhang, YA Wilson, LJ Oyston, J Cotterell, Y Qi, TM Khuong, N Bakhshi, Y Planchenault, DT Browman, MT Lau, TA Cole, AC Wong, SJ Simpson, AR Cole, JM Penninger, H Herzog, GG Neely. Cell Metab. 2016 Jul 12;24 (1) 75-90.

Non-nutritive sweeteners like sucralose are consumed by billions of people. While animal and human studies have demonstrated a link between synthetic sweetener consumption and metabolic dysregulation, the mechanisms responsible remain unknown.

In this study a diet supplemented with sucralose to investigate the long-term effects of sweet/energy imbalance was used. In flies, chronic sweet/energy imbalance promoted hyperactivity, insomnia, glucose intolerance, enhanced sweet taste perception, and a sustained increase in food and calories consumed, effects that are reversed upon sucralose removal. Mechanistically, this response was mapped to the ancient insulin, catecholamine, and NPF/NPY systems and the energy sensor AMPK, which together comprise a novel neuronal starvation response pathway. Interestingly, chronic sweet/energy imbalance promoted increased food intake in mammals as well, and this also occurs through an NPY-dependent mechanism. Together, this data show that chronic consumption of a sweet/energy imbalanced diet triggers a conserved neuronal fasting response and increases the motivation to eat.

15. Editor's Comment

This study sought to investigate the long-term effects of a non-nutritive sweetener, sucralose, on sweet/energy imbalance in flies and mice. Among the flies and mice with a sucralose-supplemented diet, food and calorie intake was increased until sucralose was removed. The investigators linked this response to neuropeptide F (NPF) in flies and neuropeptide Y (NPY) in mice, two appetite-stimulating neurotransmitters, which act through AMP-activated protein kinase (AMPK). Together, these proteins form a neuronal starvation response pathway that is triggered by long-term consumption of sucralose.

Sucralose consumption initiates a neuronal starvation response reliant on NPF/NPY and AMPK signalling.

Maternal gestational diabetes and childhood obesity at age 9–11: results of a multinational study.

Zhao P, Liu E, Qiao Y, et al; for the ISCOLE Research Group. Diabetologia. 2016. doi:10.1007/s00125-016-4062-9

To learn more, researchers evaluated data from the International Study of Childhood Obesity, Lifestyle, and the Environment (ISCOLE) — a multinational, cross-sectional study conducted at sites in 12 countries. Complete data were available for 4740 of the 7372 children who participated in the study. A breakdown of the number of participants aged 9 to 11 years with complete data per country is as follows: 386 in Australia, 354 in Brazil, 443 in Canada, 413 in China, 700 in Colombia, 401 in Finland, 414 in India, 289 in Kenya, 533 in Portugal, 120 in South Africa, 324 in the United Kingdom, and 363 in the United States.

About 4% of mothers had gestational diabetes, according to the study results, with 12.3% of children having childhood obesity, 9.9% having central obesity, and 8.1% having high body fat.

The researchers found that children born to mothers with gestational diabetes vs no gestational diabetes had a 53% increased risk for obesity (odds ratio [OR], 1.53; 95% CI, 1.03-2.27), a 73% increased risk for central obesity (OR, 1.73; 95% CI, 1.14-2.62), and a 42% increased risk for high body fat (OR, 1.42; 95% CI, 0.90-2.26).

Adjustments were made for maternal age at delivery, education, infant feeding mode, gestational age, number of younger siblings, child unhealthy diet pattern scores, moderate-to-vigorous physical activity, sleeping time, sedentary time, sex, and birth weight.

After further adjustment for current maternal BMI, however, the positive association remained significant for central obesity but was not significant for obesity and high fat.

The researchers noted that how gestational diabetes affects risk for obesity in children is not fully understood, but suggested that the association may be related to how the condition affects fetal growth.

Exposure to maternal diabetes is associated with excess fetal growth in utero, possibly mainly due to an increase in fetal fat mass and alterations in fetal hormone levels, they wrote, explaining that increases in blood sugar, insulin, and leptin in offspring, as well as genetics, may also play a role.

This study is the first to evaluate the association between gestational diabetes and childhood obesity using such widespread, multinational data and the researchers found that maternal gestational diabetes was associated with an increased risk of childhood obesity among children aged 9-11 years from 12 countries, but this association was not fully independent of maternal BMI."

The researchers also cited several study limitations, including its cross-sectional design, a lack of data on maternal prepregnancy BMI and gestational weight gain, self-reported information of certain factors like gestational and child's birth weight, and inconsistent criteria for diagnosing gestational diabetes across study sites.

16. Editor's Comment

Exposure to hyperglycaemia during pregnancy has been linked to adverse outcomes in offspring. This suggests that this exposure, such as that seen with gestational diabetes, may also affect a child's weight after birth.

With the increase in childhood obesity seen around the world, researchers have begun looking at prenatal, perinatal, and postnatal environmental factors. Some studies have indicated that a relationship may exist between the gestational diabetes and a child's weight, but the relationship still remains unclear.

Blindness Due to Diabetic Retinopathy Surges Worldwide.

Janet L Leasher et al. Diabetes Care. 2016; 39: 1643-1649

The number of people with visual impairment due to DR represents an increasing proportion of all cases of blindness and moderate to severe visual impairment. In all, the researchers found, DR was responsible in one of every 39 cases of blindness and one of every 52 cases of visual impairment in 2010. With the alarming prevalence of vision loss due to diabetes rising more than two-thirds in the past 20 years, the precipitous global epidemic of diabetes must be addressed.

In the Global Burden of Disease Study, blindness was defined as presenting visual acuity below 3/60 and moderate to severe visual impairment as presenting visual acuity below 6/18 but 3/60 or greater. Data were collected from 14 countries in Australasia, Central and Western Europe, North America, the Caribbean, Latin America, Oceania, and South, East, and Southeast Asia.

In 2010 worldwide, approximately 32.4 million people were blind and 191 million people were visually impaired. Of those, DR was responsible for 833,690 cases of blindness and 3.7 million of visual impairment. From 1990 to 2010, the number of people with DR-induced blindness increased by approximately 27% and the number with DR-related visual impairment by 64%.

By percentage, DR caused 2.6% of all cases of blindness and 1.9% of all visual impairment in 2010, up from 2.1% and 1.3%, respectively, in 1990. The percentage of blindness caused by DR in 2010 ranged from less than 2% in Southeast Asia and Oceania to 5.5% or greater in southern Latin America.

In general, the percentage of blindness and visual impairment attributable to DR was lower in low-income regions with younger populations such as East and Southeast Asia and higher in high-income parts of the world, with older populations, including North America and Western Europe. A possible reason is that low-income regions may have a higher percentage of untreated cataracts or refractive error–related visual impairment, thereby reducing the proportion attributable to DR, the authors suggest. Also, in regions with poor access to medical services, people with diabetes may not live long enough to experience DR, they point out.

As unfortunately, diabetic retinopathy usually does not have any symptoms in the early stages,people diagnosed with diabetes should have a dilated eye health exam at least every year and be advised by their eye care practitioner for their personal situation. Patients should work closely with their healthcare provider to determine the best methods to control their blood sugar levels.

Useful strategies include the following:

- Develop evidence-based, cost-effective DR screening strategies.
- Improve systemic risk-factor control (such as glucose and blood pressure).
- Increase health education and awareness of the risk of DR-related visual loss.
- Prevent and treat DR through expanded use of laser treatments, intravitreal steroid injections, and anti-VEGF drugs.
- Reduce regional differences in screening and management of diabetes and DR, socioeconomic factors, and medical infrastructure.

17. Editor's Comment

Visual impairment due to diabetic retinopathy (DR) is rising worldwide, and diabetic eye disease is now the fifth most common cause of blindness, new research shows. The findings, from a meta-analysis of all available population-based studies performed worldwide from 1990 to 2012 for the Global Burden of Disease (GBD) Study 2010, were published in the September 2016 issue of *Diabetes* Care by Janet L Leasher et al. from Florida.The report is very alarming and must begiven due care to prevent blindness.

Genetic Predictors of Cardiovascular Mortality During Intensive Glycemic Control In Type 2 Diabetes: Findings From the ACCORD Clinical Trial

H Gao, ML Morieri, J Skupien, S Marvel, G Paré, GC Mannino, P Buranasupkajorn, C Mendonca, T Hastings, SM Marcovina, RJ Sigal, HC Gerstein, MJ Wagner, AA Motsinger-Reif, JB Buse, P Kraft, JC Mychaleckyj, A Doria. Diabetes Care 2016 Aug 15; [EPub Ahead of Print], HS Shah .

Genetic Markers Reveal Link Between CV Mortality and Intensive Glycemic Control in Diabetic Patients. A vexing controversy in cardiovascular endocrinology concerns whether intensive glycemic control is cardioprotective. While findings from the DCCT-EDIC trials in type 1 diabetes and the UKPDS trial in type 2 diabetes suggest this is the case, individual randomized controlled trials in type 2 diabetes (ACCORD, ADVANCE, VADT) have not been conclusive, even if meta-analyses of these trials also support the glucose hypothesis. In particular, participants in the ACCORD trial randomized to the intensive treatment arm experienced fewer cardiovascular events but paradoxically had increased mortality, attributed to cardiovascular causes.

In the present analysis, the authors used a genome-wide approach to identify genetic predictors of cardiovascular mortality in the ACCORD intensive treatment arm. They report two such loci that exceed the prespecified genome-wide significance threshold, at 10q26 and 5q13; these variants had no detectable effect in the conventional treatment arm, indicating a gene × glycemic treatment interaction. Carriers of two or more risk alleles at these two loci had a threefold higher risk of cardiovascular mortality when receiving intensive glycemic treatment, whereas carriers of the four protective alternate alleles were fourfold more likely to benefit from intensive glycemic treatment.

Notably, these findings were consistent with independent analyses in a clinical cohort from the Joslin Diabetes Center and in the ORIGIN clinical trial. If confirmed elsewhere, genetic profiling may become useful in stratifying people with type 2 diabetes into tiers of glycemic control for cardiovascular protection.

This study targeted to identify genetic determinants of increased cardiovascular mortality among subjects with type 2 diabetes who underwent intensive glycemic therapy in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.

A total of 6.8 million common variants were analyzed for genome-wide association with cardiovascular mortality among 2,667 self-reported white subjects in the ACCORD intensive treatment arm. Significant loci were examined in the entire ACCORD white genetic dataset (n = 5,360) for their modulation of cardiovascular responses to glycemic treatment assignment, and in a Joslin Clinic cohort (n = 422) for their interaction with long-term glycemic control on cardiovascular mortality.

Two loci, at 10q26 and 5q13, attained genome-wide significance as determinants of cardiovascular mortality in the ACCORD intensive arm ($P = 9.8 \times 10 (-9)$ and $P = 2 \times 10 (-8)$, respectively). A genetic risk score (GRS) defined by the two variants was a significant modulator of cardiovascular mortality response to treatment assignment in the entire ACCORD white genetic dataset. Participants with GRS = 0 experienced a fourfold reduction in cardiovascular mortality in response to intensive treatment (hazard ratio [HR] 0.24 [95% CI 0.07-0.86]), those with GRS = 1 experienced no difference (HR 0.92 [95% CI 0.54-1.56]), and those with GRS ≥2 experienced a threefold increase (HR 3.08 [95% CI 1.82-5.21]). The modulatory effect of the GRS on the association between glycemic control and cardiovascular mortality was confirmed in the Joslin cohort (P = 0.029).

Two genetic variants predict the cardiovascular effects of intensive glycemic control in ACCORD. Further studies are warranted to determine whether these findings can be translated into new strategies to prevent cardiovascular complications of diabetes.

18. Editor's Comment

A link between two genetic markers and cardiovascular mortality in diabetic patients was established and may predict if patients are likely to receive benefit or harm from intensive glycaemic control. Participants experienced a fourfold reduction (genetic risk score [GRS], 0; HR, 0.24), no change (GRS, 1; HR, 0.92), or a threefold increase (GRS, ≥2; HR, 3.08) in cardiovascular mortality. Results from the Joslin cohort confirmed the effect of GRS on the link between intervention and cardiovascular mortality (P = 0.029).

Pioglitazone Use and Risk of Bladder Cancer in Patients With Type 2 Diabetes: Retrospective Cohort Study Using Datasets From Four European Countries

P Korhonen, EM Heintjes, R Williams, F Hoti, S Christopher, M Majak, L Kool-Houweling, H Strongman, M Linder, P Dolin, S Bahmanyar. BMJ 2016 Aug 01; 354 (xx) i3903,

To evaluate the association between pioglitazone use and bladder cancer risk in patients with type 2 diabetes this retrospective cohort study using propensity score matched cohorts was done. Healthcare databases from Finland, the Netherlands, Sweden, and the United Kingdom. Data comprised country specific datasets of linked records on prescriptions, hospitals, general practitioners, cancer, and deaths.

Patients with type 2 diabetes who initiated pioglitazone (n=56 337) matched with patients with type 2 diabetes in the same country exposed to diabetes drug treatments other than pioglitazone (n=317 109). Two matched cohorts were created, using a 1:1 fixed ratio (nearest match cohort) and a 1:10 variable ratio (multiple match cohort). Patients were matched on treatment history and propensity scores accounting for several variables associated with pioglitazone initiation.

Hazard ratios and 95% confidence intervals were estimated by Cox's proportional hazards model with adjustments for relevant confounders. To assess the robustness of the findings, several sensitivity and stratified analyses were performed.

In the cohort exposed to pioglitazone treatment, 130 bladder cancers occurred over a mean follow-up time of 2.9 years. In the nearest match and multiple match cohorts not exposed to pioglitazone treatment, 153 and 970 bladder cancers were recorded, with a mean follow-up time of 2.8 and 2.9 years, respectively. With regards to bladder cancer risk, the adjusted hazard ratio for patients ever exposed versus never exposed to pioglitazone was 0.99 (95% confidence interval 0.75 to 1.30) and 1.00 (0.83 to 1.21) in the nearest and multiple match cohorts, respectively. Increasing duration of pioglitazone use and increasing cumulative dose were not associated with risk of bladder cancer (>48 months of pioglitazone use, adjusted hazard ratio 0.86 (0.44 to 1.66); >40 000 mg cumulative dose, 0.65 (0.33 to 1.26) in the nearest match cohort).

This study shows no evidence of an association between ever use of pioglitzone and risk of bladder cancer compared with never use, which is consistent with results from other recent studies that also included a long follow-up period.

19. Editor's Comment

This large study of patients with type 2 diabetes taking pioglitazone (n = 56,337) and a different drug therapy (n = 317,109) investigated the association with the risk of bladder cancer. Increasing the dosage (>40,000-mg cumulative dose) and length of time pioglitazone was administered (>48 months), did not reveal a correlation with the risk of bladder cancer.There is no evidence that pioglitazone is linked with the risk of bladder cancer in diabetic patients, a fact borne out by recent studies.

Antibiotic-mediated gut microbiome perturbation accelerates development of type 1 diabetes in mice

Alexandra E. Livanos et al. Nature Microbiology 1, Article number: 16140.

The study group looked at the effects of antibiotics on non-obese mice that were susceptible to type 1 diabetes. The team used very young mice, similar in age to a 6- month to 1-year old child. The mice were given pulsed antibiotic therapy (three doses at different time periods), a continuous but very low dose of antibiotics, or no antibiotics.

Mice exposed to the pulsed therapy were twice as likely to develop type 1 diabetes as mice that got no antibiotics. Probably, the antibiotics led to a change in the microbiome in the gut. Those changes resulted in other changes, including alterations in T cells. That, in turn, led to increased inflammation in the insulin-producing islet cells of the pancreas. The researchers also transferred some of the changed gut microbiota from the antibiotic-exposed mice to two other groups of mice. This increased the risk of type 1 diabetes in one group, but not the other.

20. Editor's Comment

These findings show that early-life antibiotic treatments alter the gut microbiota and its metabolic capacities, intestinal gene expression, and T-cell populations, accelerating type 1 diabetes onset in non-obese diabetic mice.

This study from an animal study raises the question, whether repeated antibiotic use in children may contribute to T1DM. Repeated treatments with antibiotics might lead to the development of type 1 diabetes in mice, according to this study.

Thousands of candles can be lighted from a single candle,
and the life of the candle will not be shortened.
Happiness never decreases by being shared.
— Buddha